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Yale University, 1987

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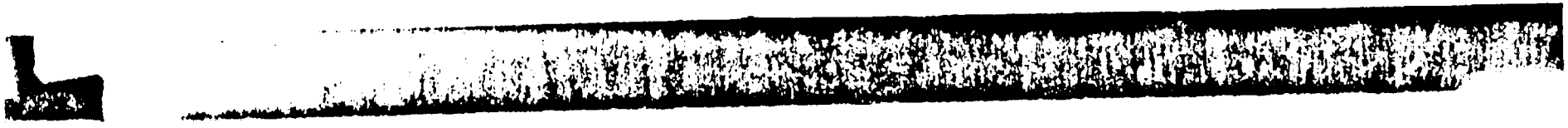

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ASSESSMENT OF THE ASSOCIATION BETWEEN PASSIVE SMOKING AND LUNG CANCER

A Dissertation

Presented to the Faculty of the Graduate School

of

Yale University

in Candidacy for the Degree of

Doctor of Philosophy

by

Luis R. Varela

May 1987

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ABSTRACT

ASSESSMENT OF THE ASSOCIATION BETWEEN PASSIVE SMOKING

AND

LUNG CANCER

Luis R. Varela

Yale University

1987

A matched case-control study was carried out to evaluate the association between exposure to environmental tobacco smoke (passive smoking) and lung cancer risk. The study population was comprised of 439 cases of lung cancer diagnosed among non-smokers. All of these cases were clinically and histologically confirmed. The corresponding controls were drawn from the New York State Department of Motor Vehicles and were individually matched to the cases on age, sex, county of residence and previous smoking history. A face-to-face interview was applied to obtain information on exposure to environmental tobacco smoke. No increase in risk was found associated with exposure to three measurements of spouse smoking, or with exposure to co-workers' smoking. Conversely, exposure to the smoke of others in the household was found to effect the risk of lung cancer. For an exposure to 150 person/years of smoking the odds ratio was found to be 1.86. This effect seems to be larger for epidermoid and small cell tumors (OR=2.83) than for adenocarcinoma and other tumors (OR=1.42). Increasing exposure to passive smoking in social situations was found to be inversely associated with the risk of lung cancer. The implication of this finding -- at odds with previous results -- is discussed.

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CHAPTER ONE

LITERATURE REVIEW

1 BACKGROUND.

In 1972, the Report to the United States Congress on the Health Consequences of Smoking for the first time gave serious consideration to the issue of the effects of environmental tobacco smoke on the non-smoker (1). That others besides smokers themselves could experience detrimental health effects due to tobacco smoke had been in the minds of many for at least a decade. Obstetricians in particular seemed to have intensified this preoccupation, by reporting that cigarette smoking among pregnant women was associated with prematurity (2) and with low birth-weight (3). Other reports attributed a whole array of adverse effects of maternal smoking on the foetus, ranging from impaired post-natal development (4,5) to congenital malformations (6).

Later studies attended to the effects of tobacco components released into the environment at large. For instance, studies in the United States (7,8), England (9), Israel (10) and other countries (11) showed how children of smoking parents had higher incidence of

respiratory infections, as well as higher hospital admission rates. Laboratory investigations showed that exposure to maternal smoking produced a defective development of pulmonary function in children, as measured by forced expiratory volume in one second (12). Finally, reports of childhood tumors associated with parental smoking appeared in the medical literature, although often with contradictory results (13-17).

That there were serious health effects on the adult passive smoker — such effects as those experienced by the smokers themselves, i.e. lung cancer — was not considered possible as recently as a decade ago. This can be gathered from the following paragraphs published in 1975 :

> "In summary, the effects of cigarette smoke on healthy non-smokers consist mainly of minor eye and throat irritation. However, people with certain heart and lung diseases (angina pectoris, COPD, allergic asthma) may suffer exacerbation of their symptoms as a result of exposure to tobacco smoke-filled environments..." (18).

> " With respect to lung cancer there is no evidence to indicate whether or not this level of exposure has an effect on the risk of developing lung cancer. However, because of the low dosage and brief exposure, it would seem unlikely that there would be a significant increase in the risk of developing lung cancer " (19).

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It is an established fact that the overall cancer risk for non-smokers is lower than the cancer risk of the general population (20-22). Compared to smokers, non-smokers' risk for cancer is about 50% lower (20). For certain sites —in particular the respiratory tract— the differences are even more dramatic. A recent study, nonetheless, has suggested that lung cancer among non-smokers may be on the rise. The suggestion of such an increase among non-smokers has focused interest in passive smoking as one of its possible causes (23). This suggestion is partly based on a better understanding of the carcinogenic qualities of both mainstream and sidestream cigarette smoke, as will be discussed at a later point in this chapter.

Enstrom (23), using data from two representative samples of lung cancer deaths and mortality statistics at the national level, found for the period between 1914 and 1968 a 15-fold increase in lung cancer death rates among white nonsmoking males aged 35-84 years. The increase was the highest for those males over 65, estimated as 30-fold. For white females the increase has been 7-fold for the 35-84 age group. These changes seem so dramatic that the possibility of errors in Enstrom's estimates has been raised: some of his data sources go as far back as 1914, and there are no means by which to check their reliability. There are also reasons to doubt the accuracy of the ascertainment of smoking status in the surveys from which the data was obtained. Moreover, the categorization of the smoking variable changes from one source of data to another, as does the proportion of self-reported smoking versus surrogate reporting, thus making the use of pooled data difficult to interpret. It has also been

proposed that some of the changes described by Enstrom may be attributed to better diagnoses and/or changes in tumor classification. However, as the author has pointed out, the trend persists after 1935, when the major changes in diagnostic criteria had been implemented. Finally, there is the possibility — as Enstrom suggests — that the rising rates indicate the intervention of other factors in the causation of lung cancer in addition to personal cigarette smoking.

Other researchers do not agree with Enstrom's findings. Garfinkel (24) computed lung cancer mortality rates for non-smoking participants in two large prospective studies. In the American Cancer Society Study, 94,000 non-smoking males and 375,000 non-smoking females were enrolled between October 1959 and March 1960. The data used by Garfinkel spans the period between the end of the enrollment phase and June 30, 1972. The second study, the Dorn Study of Veterans, was initiated in 1954 with the mailing of questionnaires to 293,000 veterans. Fifty four thousands respondents reported themselves to be non-smokers. The follow-up period ended in 1969. Mortality rates for non-smokers in both of the groups studied were estimated, mainly through the use of death certificates. Rates were adjusted to the United States adult population of 1965. Garfinkel was unable to detect any increase in mortality due to lung cancer for three four-year periods between the years 1960-1972. Nevertheless, he reported a slight difference (although not statistically significant) in lung cancer risk for non-smoking women married to smokers, as compared to non-smoking women married to non-smokers. This was probably the first population study to consider such an association. The results will be discussed in the next section of this chapter.

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2 EPIDEMIOLOGIC STUDIES.

Controversial reports on lung cancer trends among non-smokers have not been discouraging enough to dismiss the hypothesis that passive smoking — also termed involuntary smoking or secondary smoking — is causally related to lung cancer. In January of 1981, the British Medical Journal published the first population study specifically addressing this issue (25). Hirayama reported the findings of a 14 year old prospective study which involved a follow-up for 91,540 non-smoking married Japanese women. One hundred and seventy four cases of lung cancer had developed in this group, for which the husband's smoking history had been collected independently. Women married to heavy smokers (>=20 cigarettes/day) showed a higher risk for lung cancer than women married to non-smokers (standardized risk ratio = 2.08). Furthermore, a statistically significant dose-response relationship was found: the relative risk for wives of ex-smokers or smokers of 1-19 cigarettes/day was 1.6; the relative risk for heavy smokers (>=20) was 2.08 (Mantel-extension X^2 test = 3.299; p, two tails = .00097. The trend was also observed when husbands' age and occupation was taken into account. The highest relative risk, 4.6, was found among women in agricultural families married to heavy smokers aged 40-59 years at time of enrollment into the study. No increase in risk for other major cancers was observed in relation to the husbands' smoking habits.

Hirayama's study received a great deal of attention among both the medical community and the lay public. His results and methods

were closely scrutinized, prompting an exchange of letters either critical or supportive of the study. The fact that the Mantel-extension test for one of the tables was calculated erroneously was particularly emphasized. A subsequent estimate obtained by rearranging the data was published subsequently (26). The new figure did not change the basic conclusion that the study factor and the disease were significantly associated. This reassurance, nonetheless, did not preclude criticism of the study on different grounds. First, the research work — started in 1966 — did not initially intend to look at the passive smoking-lung cancer association. This particular feature of the study might have affected the quality of the information in several opposite ways. On the one hand, it may be that the likelihood of bias in "reporting" or "interviewing" was less than if a well-developed hypothesis was being tested. This is because the study subjects, as well as the interviewers, were obviously blind to a hypothesis which was non-existent at the time of data collection. On the other hand, we should consider that the research, not initially intended to study the effects of passive smoking, may not have been as thorough in the ascertainment of exposure to passive smoking as would be necessary to detect a moderate or small effect. This latter point is not worrisome, however, since it would have resulted in a conservative estimate of the effect.

Secondly, in the original publication by Hirayama no details are given on the way in which deaths were ascertained, nor was there information available on the degree of pathological confirmation of the cancer cases. It is only through subsequent publications that we

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learn that in a subsample of 23 cases, 17 were adenocarcinomas. Since smoking has been postulated to be associated with specific histologic types this information would seem crucial.

Despite the drawbacks mentioned above, there are certain features about Hirayama's study that make it unique and probably very difficult to replicate. The prospective design involving a large population in more than one geographic region is certainly an asset. Also advantageous is the fact that the study was carried out in a traditional society where smoking habits of women are low, thus diminishing the probabilities of including erroneously classified women who developed cancer of the lung as a consequence of their own smoking. Also, in such a setting marriages may last longer, houses are certainly much smaller, and socializing for women usually takes place in the company of their husbands. All of the above suggests that quantification of the husbands' smoking habits may indeed be a good measure of exposure to secondhand smoke.

Also in 1981, Trichopoulos et. al. published the preliminary results of a study conducted in Greece (27). Using a case control design, they assembled a group of 40 non-smoking women diagnosed with lung cancer in three large Athens hospitals. The patients were interviewed regarding their husbands' smoking habits and were compared with the husbands' smoking habits of 149 non-smoking hospital controls. The controls were orthopedic patients who did not differ significantly from the cases with regard to age, education, duration of marriage, occupation or residency. The odds ratio for women married

to ex-smokers was 1.8; it was 2.4 if they were married to current smokers of 1-20 cigarettes/day; and 3.4 if married to current smokers of more than 20 cigarettes/day. This dose-response trend was found to be statistically significant (Chi-sq for linear trend = 6.45, p(2 tails) < .02.). When exposure to husbands' smoking over the course of the marriage was assessed a similar trend was observed. Estimated odds ratios were 2.5 for those exposed to 100 - 299 thousand cigarettes and 3.0 for those exposed to 300 thousand or more cigarettes (Chi-sq for linear trend = 6.56, p (2 tail) < .02).. This linear trend was identical in both group of cases: those with citological confirmation of tumor and those with clinical diagnosis only.

A later report of Trichopoulos' study in 1983 added nearly as many cases, and 500 more controls, to the study subjects (28). The results were substantially the same: odds ratio of 2.4 for wives of smokers of less than 20 cigarettes/day, and odds ratio of 3.4 for women married to smokers of more than 20 cigarettes per day (Chi-sq for linear trend = 6.7, p (2 tail) = .01).

The Greek study, although not entirely comparable to that of Hirayama, shows similar results. It also shares some of the advantages of the latter, namely, those concerning family structure and family social life, together with their implications on the assessment of exposure, as enumerated above. Different methodological problems, however, ought to be considered. For instance, the study group is small and the degree of pathological confirmation poor (only 65% had a citological or histological diagnosis). The study subjects (non-

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smoking women with lung cancer) represent about 78% of all the female lung cancer cases diagnosed in the participating hospitals. As is mentioned in a subsequent section of this chapter (see: Histologic Type and Lung Cancer) the proportion of non-smoking patients in other series of lung cancer cases has been established at about 10% for women. The excessively high proportion reported by Trichopoulos suggests that some of his cases may indeed have been smokers who did not admit to their tobacco habits for social or other reasons. Or, although the proposition is somewhat unlikely, it may be that non-smoking women with lung cancer in Greece are more likely to be hospitalized than in other parts of the world.

In addition, the fact that both cases and controls were interviewed by a single, unblinded researcher, points toward the possibility of misclassification of exposure. On the other hand, the attempt to assess exposure according to spouses' smoking habits during the total length of married life may have provided more complete ascertainment of exposure.

Pelayo Correa et. al., using a case-control design, assessed the risk of lung cancer for both non-smoking men and women with regard to the smoking habits of their spouses and parents (29). They found an odds ratio of 2.0 for 8 men married to women who smoked more than one pack of cigarettes a year. The corresponding odds ratio for 22 women married to smoking men was 2.07. Neither was statistically significant. After controlling for the spouses' smoking habit, maternal (but not paternal) smoking was associated with a higher risk

of lung cancer, as indicated by an odds ratio of 1.47 (Opposite results on this parental smoking-lung cancer association have been reported by Sandler, et. al.. Those results will be discussed latter in this chapter). The effect observed, however, was neither significant nor seemed to be dose-related. When exposure to both parents' smoking was combined, the odds ratio became significant only for those cases exposed to = > 41 packs of cigarettes per year (OR = 3.11, $\hat{p} < .05$).

Important drawbacks can be found in the study by Pelayo Correa et. al.. Its main disadvantage is the fact that the number of participants is so small that any of the possible strengths of the study -- such as the 100% histologic confirmation of diagnosis -- fail to compensate for this weakness.

A more recent epidemiologic study on the lung cancer-passive smoking relationship was carried out by Garfinkel, Auerbach and Joubert (30). Their group of cases was comprised of all female non-smoking lung cancer patients diagnosed in three hospitals in New Jersey and one hospital in Ohio. Women diagnosed with colon cancer served as controls. Three controls were matched to each case on the basis of age (←5 years) and hospital of diagnosis. Pathology slides for both cases and controls were reviewed blindly in order to confirm the diagnosis. One hundred and thirty four lung cancer cases and 402 controls were then interviewed regarding the smoking habits of their husbands. Current smoking habits, number of cigarettes smoked at home, and number of years the husbands had smoked were assessed.

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Similarly, women were questioned about the number of hours a day they had been exposed to the smoke of others in the past 5 and 25 years.

It was found that women married to smokers of 40 or more cigarettes per day had an odds ratio of 1.99 (95% CL:1.13-3.50) as compared to those married to non-smokers. If half that amount of cigarettes was smoked at home, the odds ratio was estimated to be 2.11 (95%CL:1.13-3.95). Similarly, an increased risk was found for those women married to men who had smoked for 20-29 years (OR ~ 2.2), but, unexpectedly, not for those married to smokers of more than 30 years. No increase of risk was found to be dependent on the number of exposure-hours in the last five and 25 years.

Using logistic regression techniques, a model was fitted to the study data. The model included terms for possible confounders and several continuous variables representing exposure. An increase in risk with increasing exposure was found for the number of cigarettes smoked by the husband at home. This trend was statistically significant at the 0.05 level.

The study by Garfinkel et. al. attempted to tackle some of the methodological problems present in the former studies on passive smoking. The authors were successful in putting together a sizable group of cases who were confirmed never-smokers and whose diagnosis was histologically confirmed. Their assessment of exposure was not limited to the smoke derived from the husbands' smoking but included that experienced at the worksite and other areas. Powerful statistical techniques (logistic regression) were used to analyze the data, producing results consistent with the findings of the two other

major studies on this topic. It seems, therefore, that the only aspect of the study that could have affected the results is that which is most difficult to evaluate: the reliability of the data collected through the interview. Even though the interviewers were supposedly blind in regard to the hypothesis of the study and the case/control status of the participants, the participants themselves were aware of their own condition. In this situation the possibility of overreporting by the cases must be borne in mind. Additionally interviews of surrogate respondents may have affected the reliability of the information about the exposure variable. In fact, Marcel (31) has shown that Garfinkel's estimates of the odds ratios vary considerably according to the type of respondent. He found that the odds ratio for lung cancer was 3.57 (95% CL: 0.84-15.28) in the subgroup in which the respondents were either a daughter or a son of the study subjects. In the subgroup in which the husband provided information on the exposure he found that the odds ratio was 0.77 (95%CL: 0.56-1.06. And finally, in the subgroup of cases who reported about their own exposure, the odds ratio was estimated to be 0.83 (95% CL: 0.58-1.38).

At the same time that this report was being prepared, two additional epidemiologic studies claiming the existence of a moderate effect of passive smoking on lung cancer risks were published. The first of these was also conducted in Japan (32). It is a case- control study, but, as was true of its predecesor, it makes use of a cohort initially defined for another purpose (the study of the effects of atomic radiation in Hiroshima and Nagasaki survivors) in order to

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obtain its study subjects. The cohort, comprised of about 110,000 people, yielded 525 cases of lung cancer between 1971 and 1980. Pathologic diagnosis were done in 57% of these. Controls were selected from the same cohort among members who had not develop lung cancer. The controls were individually matched to the cases with regard to year of birth (+- 2 yrs), residence, sex, vital status, and whether or not they had belonged to the conort subgroup that underwent biennial medical examinations. Information was obtained for 428 cases and 957 controls. However, only 13 male cases and 94 female cases occurred among non-smokers. Among the non-smoking males the odds ratio associated with having a spouse who smoked was 1.8 (90% CL: 0.5 - 5.6). For females the corresponding figure was 1.5 (90% CL: 1.0 - 2.5). In addition, females showed an increase in risk of lung cancer with the increasing number of cigarettes smoked by the husband; the odds ratio being greater than 2.0 for the highest exposure category. The test of linear trend, however, was not statistically significant at the 0.05 level. Likewise, another measure of husbands' smoking -- the number of years the husband smoked -- was not statistically significant. Finally, their results showed that non-smoking women who had been exposed to the husbands' smoking in the last 10 years had a lower risk (OR = 1.3, 90% CL: 0.9 - 2.4) than those women exposed within the last 10 years (OR = 1.8, 90% CL: 1.0 - 3.2).

Some of the above estimates are consistent in their magnitude (if not in their statistical significance) with the results of the first Japanese study, as well as with the other studies on passive smoking. However, this subsequent study equally shares in some of the

methodologic problems that cast doubts over their results. One such problem is the poor rate of histologic confirmation. The authors, in trying to circumvent this problem, carried out separate analysis for those with pathologic diagnosis, as well as those without it. An undesired consequence of such approach, however, is the loss of statistical power due to the resulting smaller groups available for estimation of the parameters. Another potentially important problem concerns the obtaining of the information about exposure. Only 22 cases and 26 controls out of the total, although not necessarily out of the non-smoking group only, were available to be interviewed. Exposure for all others was assessed through the interviewing of surrogate respondents. Even though the distribution of types of surrogate respondents was similar for cases and controls, it cannot be ensured that selective recall was eliminated. A final point concerns the pecularities of the study group, survivors of the atomic explosions of Hiroshima and Nagasaki. Since both cases and controls were equal in that regard, we do not question the internal validity of the findings beyond the methodologic problems mentioned. However, we should be cautious in any attempt to extrapolate these results to the general population. It could be that the effect observed is only a product of a synergistic effect between radiation and exposure to tobacco smoke. This synergy, of course, would not be possible in the general population since on the whole it lacks exposure to the levels of radiation experienced by the subjects in this study. Finally, the authors of this study have been less than conservative in establishing that level of statistical significance which they are willing to accept. Values of p between 0.05 and 0.1 are reported as

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significant. Additionally, 90% confidence limits are reported instead of the conventional 95% CL. Although from a methodologic or statistical point of view there is nothing wrong with this approach, it raises concern that researchers, in order to detect and report "significant" effects, may take the risk of accepting a greater role of chance in their findings than that which is conventionally deemed appropriate.

The second most recently published article is based on the pooled data from three case-control studies (33). Ninety nine histologically confirmed lung cancer cases and 736 controls comprised the study group. These were all the participants in studies carried out in Louisiana, Texas and New Jersey who reported themselves to be never smokers. Due to the fact that the data came from three different sources, the type and level of detail of the information about passive smoking was not uniform for all study subjects. Nevertheless, information about exposure in the home environment was either available or could easily be estimated for everybody. Analysis of the data showed no increase in risk of lung cancer associated with ever having lived with a smoker (OR = 1.0, 95% CL: 0.64 - 1.56). Controlling in the analysis for the variables age, sex and study area, did not unveil any relationship either. The number of years lived with a smoker was not found to affect the risk of lung cancer. Conversely, some positive findings were described for exposure to the spouse's smoking. A smoking spouse was found to be associated with an odds ratio of 1.47 (not statistically significant). The number of cigarettes smoked a week by the spouse showed a linear relationship

with risk of lung cancer despite the fact that the estimates for each level of exposure, individually, did not reach statistical significance. The highest and only significant effect was reported for women 63 years or older married to blue collar workers who were heavy smokers (280 or more cigarettes/week).

3 OTHER STUDIES.

Despite the fact some studies were not intended specifically to look at the association between passive smoking and lung cancer (or at least this relationship was not the main focus of their inquiry), they provide information to contend that such connection is feasible. The study on lung cancer trends published by Garfinkel (24), as well as a study by Kabat and Wynder (34) on the histopathologic patterns of lung cancer in non-smokers, both fall into this category.

Similarly, studies linking passive smoking with cancers other than that of the lung can be helpful in delineating the carcinogenic potential of sidestream smoke. The studies by Sandler and colleagues (35-37) belong to this group.

Garfinkel (24) in his analysis of the American Cancer Society study compared the mortality rates for non-smoking women married to non-smokers with the mortality rate of non-smoking women married to smokers. It was found that women whose husbands smoked less than 20 cigarettes per day had a 27% higher lung cancer mortality rate than

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women married to non-smokers. The rate was only 10% higher for those married to a smoker of more than 20 cigarettes per day. When confounding variables were taken into account (age, race, education, residence and husbands' occupation), the excess risk was 37% and 4%, respectively. None of these findings were statistically significant. However, the results have to be interpreted with great caution because the study was never designed to obtain information on passive smoking. Furthermore, whatever smoking information was available corresponded only to the exposure at time of enrollment into the study.

Kabat and Wynder (34) assessed exposure to secondary smoke in a subset of non-smoking patients included in a large study of tobacco-related cancers. Out of 25 male cases six reported exposure to other people's smoke at home, as compared to 5 out of 25 controls. Eighteen of these cases reported exposure at work versus 11 of the controls. This last difference was barely statistically significant. Among the female group (n=53) about the same proportion of cases and controls were exposed to other people's smoke at home and work; consequently, the association with lung cancer was not statistically significant.

Sandler, et. al. reported the results of a case-control study involving 518 cancer patients (all sites, except basal-cell cancer of the skin) and 518 controls. In three separate publications the authors assessed the association between these cancers and: 1) exposure in childhood and adult life to the smoking of all household members who smoked (35), 2) early life exposure to parental smoking (36), and 3) exposure in adulthood as a result of spouse's smoking (37). In the first of these studies, the odds ratio for those exposed to one smoker

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in the household was found to be 1.5. If exposed to the smoke of two individuals, the odds ratio increased to 2.3, and to 2.8 if exposed to the smoke produced by three smokers. This trend was statistically significant ($p < 0.01$). However, it should be noted that an increase in risk was also observed for active smokers who had been exposed to the smoke of others in the household.

The overall cancer risk for all study subjects (passive, as well as active, smokers) was reported to be elevated in both of two circumstances: when exposure to secondary smoked had ocurred during childhood only (OR=1.6), and when the exposure took place in adult life exclusively (OR=1.5). For an individual exposed in both periods of life, the odds ratio exceeded two (OR=2.7).

For the second report, information on smoking habits of both parents was obtained for almost all the cases (n=438) and almost all of the controls (n=470). For all cancer sites the risk was increased for all the cases (again, passive and active smokers combined) if the father was a smoker (OR=1.5, 95%CL: 1.1-2.0). Maternal smoking, however, did not seem to increase the overall cancer risk (OR= 1.1, 95%CL: 0.7-1.6). Similarly, the risk for lung cancer was increased in those exposed to the father's smoke (OR=1.8, 95%CL: 0.5-6.6), but not to the mother's (OR=0.9, 95%CL: 0.4-2.1).

Lastly, when cancer risk was assessed in relation to the spouses' smoking habits, it was found that individuals married to smokers had 1.6 times the risk of individuals married to non-smokers ($p<0.01$). This difference could not be accounted for by differences in age,

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race, sex, education, or occupation between cases and controls. When site-specific cancer risk was assessed, the authors found that exposed individuals (those married to smokers) were at higher risk for cancer of the breast (OR=1.8), of the female genital organs (OR=1.8), and of the endocrine system (OR=3.2). Based on a small number of cases (n=22) it was found that passive smokers showed 1.9 times the risk for lung cancer than those not exposed to secondhand smoke. This finding did not reach statistical significance.

There are mainly three problematic features in Sandler's publications that deserve some attention. The first relates to the way in which the results have been presented. In many instances the risk for cancer associated with passive smoking is presented for the whole study group, comprising non-smokers as well as smokers. Although the latter group can be considered passive smokers of their own secondary smoke -- as well as of the smoke that others produce -- their inclusion seems inappropiate, since the overwhelming effects due to direct smoking would tend to distort the effect due exclusively to passive smoking. Some tables, however, do make the distinction between the two groups, and those are the ones that are most informative. Secondly, confounding variables that may explain the observed associations were not taken into account. Some of these variables are exposure to alcohol, to occupational hazards, to drugs, and to sexual and reproductive behavior variables. Thirdly and lastly, the fact that an association was found between passive smoking and cancers not previously described as tobacco-related (breast, endocrine system) raises some suspicion. This finding may be a

consequence of the inability to control for confounders, as mentioned above.

In addition to the epidemiologic studies, laboratory investigations, along with clinical and pathological observations, have supported the hypothesis that lung cancer and passive smoking indeed may be associated. The most relevant literature in these areas is discussed in the following paragraphs.

4 LABORATORY INVESTIGATIONS

Both observational and experimental laboratory studies have produced valuable information on the biological plausability of the health effects of passive smoking. The most important findings are related to the identification of carcinogenic substances in sidestream smoke and the ability of some sidestream smoke components to enter the organism of the passive smoker (38-45). Cigarette smoke contains over one thousand substances (46). Many of them, including carcinogens, are present in even higher concentrations in sidestream smoke than mainstream smoke. For instance, Dimethylnitrosamine, a potent carcinogen in animals, is 52 times more concentrated in sidestream smoke (47-48) Brunemann, et. al. (49) have estimated that a non-smoker who spends one hour in a smoky room may inhale nitrosamines in quantities equivalent to smoking about 15 cigarettes. Benzo(a)pirene, another known carcinogen in men and animals, is present 3.4 times as much in sidestream smoke. Furthermore, one cigarette may release up

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to 100 ng of that substance into the air (46).

But how much exposure to these substances does the regular non-smoking person really experience? This has been very difficult to quantify. The concentrations of tobacco components in the environment depends on numerous factors. The amount of tobacco consumed, the volume of ambient air, the size of the room where smoking takes place, and the type and amount of ventilation in an enclosed space are some of the many variables that affect smoke intake. The proximity of the passive smoker to the source of smoke and his/her pattern of inhalation may also affect actual exposure (48). Similarly, the smoking patterns of the individuals who do the smoking need to be considered. For instance, the variation in puff frequency, puff duration and puff volume are known to affect both the chemical composition of sidestream smoke and its biological activity (50-54). Even the smoker's health status seem to affect the way in which sidestream smoke is produced (55). In fact, it is the sidestream smoke that has been modified by the above and other factors that constitute the real exposure to the passive smoker. Some authors prefer to refer to this as environmental tobacco smoke rather than sidestream smoke.

Despite these difficulties, some studies have attempted to quantify actual exposure by measuring tobacco metabolites in body products. Serum thyocianate and cotinine are found in the blood, urine, serum and saliva of the passive smoker (45, 56-60). Although thyocianate may result from other sources — i.e. leafy vegetables —

cotinine is a specific marker for exposure to tobacco smoke and therefore its presence in the non-smokers is taken as evidence of passive inhalation. In one experiment a researcher was also able to identify mutagenic substances in the urine of subjects exposed to smoke in a poorly ventilated room (40).

Studies aimed at determining the specific deposition of environmental smoke components in the lung tissues are very scanty. In theory, the biological features of the anatomy and physiology of the human respiratory system, and the physical and chemical characteristics of sidestream smoke, suggest that such deposition takes place. The extent of it, however, has been a matter of debate. Different authors have reported high levels of smoke bronchial deposition ranging from 11% (61-62) to 80% (63).

Conversely, Repace and Lowry (64) think that most passive smokers are exposed to a minimal amount of smoke, perhaps no more than the equivalent of one cigarette per day. It has been suggested that such an exposure conveys a negligible risk (65). With respect to this, it should be noted that no treshold level of exposure for the development of lung cancer has been established. Therefore, any level of exposure — including the low level attained by passive smoking — should be considered potentially able to elicit a carcinogenic response.

Another series of studies have been aimed to detect the effects of passive smoking in the respiratory function of passive smokers. This is particularly relevant since some authors think that an

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impaired respiratory function is in itself a risk factor for lung cancer (66-69). In France, Kauffman (68) et. al. compared spirometric measurements between two types of non-smokers, exposed and non-exposed to secondary smoke. They found that both men and women married to smokers of >= 10 g of tobacco a day had a significantly lower forced mid-expiratory flow rate (FEF 25-75) than those married to non-smokers. In addition, women in the exposed group showed a decrease in forced expiratory volume in one second (FEV 1). The study carefully controlled for confounding variables such as age, social class, education, family size and air pollution.

White and Froeb (69) conducted a study in which the effects of passive smoking in the workplace were assessed. It was found that the decrease in forced mid-expiratory and end expiratory (FEF 25-75 and FEF 75-85) among passive smokers was comparable to the decrease observed in light smokers.

The effects of passive smoking on the pulmonary function of children as measured by spirometric measurements was mentioned in a preceeding section (12); they have been confirmed recently in a study by Chen and Li conducted in Shanghai (70).

Different carcinogenic mechanisms have been postulated for smoke both mainstream and environmental. These mechanisms are thought to explain the development of lung cancer among passive smokers even if, as some believe, the smoke dose conferred by passive smoking is low. Such mechanisms are also believed to be related to the different histologic patterns observed in smokers and non-smokers. According to

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the first hypothesis, carcinogens present in environmental smoke would have the ability to produce adenocarcinoma, the type of cancer more common among non-smokers. Since volatile compounds are more likely to be absorbed by the passive smoker, it is precisely in those compounds where carcinogenic properties would reside. Furthermore, since volatile carcinogens would be able to reach the distal ends of the bronchial tree, one would expect to find more tumors in the periphery of the lungs of non-smoking cases than in smoking cases. Wynder and Goodman (67) suggest that, indeed, this anatomical preference is present among non-smokers.

The second (most widely accepted) hypothesis proposes that environmental tobacco smoke and mainstream smoke have exactly the same carcinogenic properties, despite the known differences in their physicochemical characteristics. Under this hypothesis, the exposure to environmental smoke is considered to be equivalent to low levels of exposure to mainstream smoke. The fact that no treshold has been established for the carcinogenic effect of maintream smoke (that is, that any level of exposure conveys a risk above that of no exposure) supports this hypothesis. Further support is provided by the observation that epidermoid and small cell carcinoma (considered by many to be the tumors more strongly related to active smoking) have been found associated with exposure to passive smoking (30,33).

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5 ANIMAL EXPERIMENTS.

Testing the hypothesis that passive smoking and lung cancer are related by means of animal experiments involves similar difficulties ascribed to the study of the carcinogenic effects of direct smoking. The search for a suitable animal model has taken many years, and while researchers are able to reproduce many of the respiratory system tumors, no one would claimed to have found an ideal model.

However, even without intending to do so, many of the experiments aimed at studing the effects of direct smoking may indeed have been testing the effects produced by passive smoking. Various species of laboratory animals (mice, rats, sytian hamsters) have been experimentally exposed to smoke-filled environments (72-75) One such study (72) now considered a classic in the field, has shown that rabbits exposed to environmental smoke may develop tracheobronchial epithelial metaplasia and dysplasia. This study, along with the others which followed it, were interpreted with much caution since they did not quite simulated the phenomenon they were intended to study (i.e. the effects of direct smoking). Different but equally important caveats should be taken into consideration when these studies are used to draw conclusions about exposure to passive smoking. For instance, we cannot be sure that exposure to smoke in a closed chamber actually simulates passive smoking, nor that the anatomy and physiology of the respiratory tract of the experimental animals would respond to secondary smoke in the same way as human's.

More recently, sophisticated equipment that produces and traps

sidestream smoke has been developed to simulate exposure to whole smoke or to its gas phase only (76). Such devices include exposure chambers for rodents, cell cultures or isolated perfused lungs, as well as mechanisms to manipulate smoke volume, dilution, and other variables to be studied. These devices are not yet part of the standard equipment of specialized laboratories, but it is likely that their introduction will produce a wealth of knowledge regarding the effects of sidestream smoke.

Lastly, many studies have presented evidence of the carcinogenic properties of tobacco components when administered through routes other than the respiratory tract. Many articles on the effects of subcutaneous injections of tobacco components (76-77), along with articles on the effects of rubbing and skin painting with tobacco compounds (76), agree that there is little reason to doubt the carcinogenic properties of tobacco smoke.

6 SMOKING AND HISTOLOGIC TYPE OF LUNG CANCER

An observation that has created a great deal of interest among researchers concerns differences found between lung cancer cases in smokers and lung cancer cases in nonsmokers. These differences pertain mainly to two factors, sex and histologic type. The relevant literature in this subject is discussed in the following paragraphs.

Among women with lung cancer there is a higher percentage of nonsmokers than among male cases. In upper New York State — as

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preliminary information for this study was being collected -- we found that nonsmoking women comprised 9.0% of all female cases, whereas nonsmoking men represented only 2.0% of all male cases. Using data published by Greenberg et. al. (78), I estimated similar figures. In their series of cases, 10.7% of the women were nonsmokers versus 3.0% of the men. From data provided by Kabat and Wynder (34) the estimated corresponding figures are 14.9% and 1.96%. Finally, Garfinkel et. al. reported that 12% of the female lung cancer cases screened for participation in their study (30) were non-smokers.

It has been suggested -- since fewer women than men smoke -- that a larger proportion of females are left suceptible to the effects of other carcinogens (including secondhand smoke) than to direct cigarette smoke. These carcinogens would be responsible for the "excess" number of nonsmoking female cases. The effects of these carcinogens in men would be masked by the overwhelming effect of direct cigarette smoke.

Histologic type has also been recognized to be associated with smoking habits. The nature of this association, however, remains controversial. As early as 1957, Doll et. al. (79) had proposed a "dose-response" relationship by showing an association between the amount of tobacco smoked and the development of epidermoid, large cell and small cell carcinoma. Other histologic types were found to be either unrelated, or only slightly related, to smoking. A few years later, Kreyberg published similar observations (80). He found an association between smoking and epidermoid, large cell and small cell

carcinomas. Similarly, he rejected an association between smoking and both adenocarcinoma and bronchioalveolar carcinoma.

From then on, no author has fully agreed with any other, presenting results that are often frankly contradictory. Weiss, et. al. (81) in a prospective study of 6,163 men, added adenocarcinoma to the list of histologic types related to smoking. Yesner (82) confirmed the association between smoking and small cell carcinoma, but not with other cell types. Auerbach found smoking habits to be equally distributed in all cell types, therefore denying any association between histology and tobacco smoke (83) Vincent concludes that adenocarcinoma and bronchioalveolar carcinoma are inversely related to smoking (84). And, more recently, two independant studies have reported that all cell types, including adenocarcinomas, are related to cigarette smoking (85).

The difficulties in interpreting the results of these studies are many. Two in particular, however, deserve to be mentioned. First, there is the problematic characteristics of the study groups. They comprise such heterogenous -- and selected -- populations that possible sample bias is difficult to ignore. Secondly, the intervention of so many pathologists in the reviewing of the slides brings to mind the likelihood of unreliability of diagnoses. It should also be added that the studies cover an extended period, the mid fifties to 1984. During this period the ability to assign lung cancer cases to specific histologic types has changed, as can be assessed by the decreasing number of cases diagnosed as

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undifferentiated cell types.

A much clearer association is found between histologic type and sex. Most studies agree that epidermoid carcinoma is more frequent in males than females. The proportion of male cases classified as epidermoid carcinomas ranges between 38% and 64%. For females, the values are between 21% and 55%. The other notable difference occurs among adenocarcinomas: this tumor is much more common among women than men. Up to 52% of all lung cancer cases in females have been reported to belong to these group, whereas 33% is the highest among men to be presented in recent studies.

The difference in smoking habits between men and women suggests that such habits may be responsible for the difference in histologic types among the sexes. Unfortunately, this has not been properly assessed in any study. Most reports deal with the sex-histologic type, or the smoking-histologic type association. The three-way interaction, sex-smoking-histologic type, remains to be studied.

CHAPTER TWO

METHODS

In April of 1982 the New York State Department of Health initiated a large study of the epidemiology of lung cancer. New York State, with approximately 10,000 cases of lung cancer reported every year to its tumor registry, provided an excellent setting for a study of this nature. The project was intended to be comprehensive, that is, to include both smoking and non-smoking lung cancer cases. Study of the group of smoking cases was limited to the clinical and pathological characteristics of lung cancer, whereas the assessment of exposure to passive smoking and other relevant environmental variables were the main study variables in the non-smoking group. The study design also called for a population based case-matched control group (this group will be described later in full detail). It is only these two latter groups — non-smoking cases and their correspondent matched controls — that will be used to assess the effect of exposure to passive smoking on the risks of lung cancer. The

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methodologic approach used to this end is the one-to-one matched case control study.

It may be pertinent to mention that the original design of the study specified that, in order to discern more precisely the effects of passive smoking on the risk of developing lung cancer, all cases included would be never smokers. Two things were clear early on, however: first, that male cases were rarely never smokers (only 2.0% of those initially screened for inclusion in the study reported to have never smoked), and second, that a sufficient number of these cases could not possibly be assembled in a reasonable period of time so as to satisfy the sample size requirements. Therefore, the eligibility criteria for cases was extended to include those who had stopped smoking at least 10 years before diagnosis. It should then be clear that when we refer in this report to the group of non-smoking cases, we are referring not only to never smokers but also to former smokers. The implications of the decision to include former smokers in the study group are discussed in the later section of this Chapter that deals with methods of analysis, as well as in Chapter Four.

1 OBJECTIVES.

The main purpose of this study was to explore the relationship between passive smoking and lung cancer in non-smokers, using a case-control approach. This was done by analyzing data collected in 439

cases of lung cancer and 439 matched "healthy" population controls.

The specific question addressed in the analysis were:

1) Is there a risk for lung cancer associated with the spouses' smoking habits?

2) Is there a risk for lung cancer associated with smoking habits of members of the household (inclusive of spouse)?

3) Is exposure to passive smoking in the workplace associated with a higher risk of lung cancer?

4) Is passive smoking in social situations associated with a higher risk of lung cancer?

5) In the event that the answer to these questions is affirmative, does the association persist after controlling for confounding variables?

6) Can a dose-response between passive smoking and lung cancer be shown in this data?

7) Are there difference in risk for men and women?

8) Are there differences in risk for never smokers and for former smokers?

9) Is there a higher risk associated with a specific lung cancer histologic type?

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2 SAMPLE SIZE.

It was estimated that a sample size of 450 cases (225 males and 225 females), together with 450 controls, would be necessary to detect a relative risk of the order reported by Hirayama (25) and Trichopoulous, et. al. (27). Preliminary information collected in the study area showed that approximately 1,200 female lung cancer cases were diagnosed in the study area every year, and that 9.0% were among never smokers. Thus, it was estimated that (allowing for a 15% refusal rate) the 225 female cases could be assembled in a period of about 30 months, roughly the time available to collect the data for the study. Since only 2.0% of men were never smokers, gathering the same number of male cases would have taken much more time than the available period allowed. As indicated above, it was such a realization that prompted the decision to include cases that had stopped smoking at least 10 years back.

The final sample size fell slightly short of the proposed number. It was comprised of the 439 cases and their 439 matched controls, for which information was complete. Among all eligible cases the response rate was close to 80%. Subtracting an additional 4.0% for physicians' refusal to let their patients participate, the total response rate can be estimated to be 76%.

3 LOCATION OF THE STUDY.

A check of the data accumulated by the New York State Tumor Registry showed that about 80% of cases of lung cancer occur among residents of the eight Standard Metropolitan Statistical Areas of Upstate New York. This locale comprises 23 counties, with approximately 125 diagnostic and/or treatment facilities. It was decided that the resources available for the study would be used more efficiently — and the logistics of the field work greatly simplified — by limiting the study to that geographic area.

4 ESTABLISHMENT OF THE CASES REPORTING SYSTEM.

The first step of the project involved setting up a reporting system in all participating hospitals. The field staff, comprised of six experienced Research Assistants, was in charge of establishing the necessary contacts within the institutions. In each hospital the Medical Records Department, the Pathology Department, and the Tumor Registry reported to our field staff all clinically and histologically diagnosed lung cancer cases, either via telephone call or during the field staff regular visits to the hospital. Cooperation from all participating hospitals was excellent, with the largest facilities reporting as frequently as once or twice a week, and the smaller ones reporting at least once a month. The New York State Cancer Registry was also screened periodically to ascertain cases that might have been

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missed by the hospital-based reporting system. Special emphasis was put by the field staff on the timeliness of the reporting, since it was necessary for the purposes of the study to obtain personal interviews with the cases before they died or became too ill to participate. The mean time elapsed between diagnosis and reporting was estimated to be 45 days, with an additional 102 days transpired before the conducting of the interview.

The reporting of a case was followed by the securing of the smoking history stated in the patients' hospital medical records. All cases reported as never smokers, former smokers or of unknown smoking status were contacted by telephone and their smoking history confirmed. Only those confirmed never smokers, or ex-smokers for at least 10 years, were considerd for inclusion in the study. All the elegibility criteria for cases are listed below.

5 ELEGIBILITY CRITERIA FOR CASES.

1) The patient must be a resident of the 23 county study area (8 SMSA of Upstate New York).

2) The patient had to be between 20 and 80 years of age.

3) The patient had to be a never smoker (smoked <= 100 cigarettes in a lifetime) or an ex-smoker (smoked <= 100 cigarettes in the last 10 years).

4) The patient should have a clinical or histological diagnosis of primary lung cancer made between July 1, 1982 and December 31, 1984.

5) The discharge diagnosis had to be confirmed by the re-examination of the pathology slides by an expert reviewer (see Histology Review in this Chapter).

Conversely, the exclusion criteria were as follows.

1) Any patient initially reported as a never or former smoker, who was later found not to comply with the definition of never and former smoker used in this study.

2) Any patient with a discharge diagnosis of primary lung cancer who, upon the re-examination of the histologic specimens, was assigned a different diagnosis.

3) Any patient not fulfilling the requirements of age, residency, or date of diagnosis.

4) Any patient for whom an individual or a physician's consent was not granted.

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6 SELECTION OF CONTROLS.

In order to provide a comparison group, each case was individually matched to a population control. The source for such controls was the State Department of Motor Vehicles files. This source was considered appropriate since it provided most of the information necesary to perform the matching. Additionally, this method was regarded as less time-consuming and more economical than other possible methods for the selecting of controls, such as random digit dialing. For each case, six potential controls were selected on the basis of age, sex, and county of residence. Upon a telephone interview, the first potential control who was found also to match the case on the basis of smoking status — and who, in addition, agreed to participate fully — was included in the study. In summary, the eligibility criteria for controls was as follows.

1) The control had to be of the same age (+ - 5 years) as the corresponding case.

2) The control had to be of the same sex as the case.

3) The control had to be a resident of the same county as the control.

4) The control had to have the same smoking history as the case. That is, both had to be either never smokers or ex-smokers for at least 10 years.

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An additional matching variable was considered at the time of conducting the interview. It concerns the matter of whether the questionnaire was responded to by the case himself/herself or, on the other hand, by a surrogate respondent. The matching on type of interview is better explained in the section of DATA COLLECTION which appears next on in this Chapter.

On the average, two potential controls had to be called until one matched the case on smoking history and was willing to participate in the study.

7 DATA COLLECTION.

Once the elegibility of cases and controls was determined, the field staff arranged a face to face interview which took approximately one hour to conduct in the patient's home. All information was collected using a pre-coded questionnaire. The questionnaire was pre-tested for a 3 month-period using patients diagnosed prior to the study period. The sections of the questionnaire that contain the items used for analysis in the present study are found in Appendix A. As would be expected, most of these questions are concerned with the measurement of exposure to passive smoking; but information on social, demographic and medical variables was also sought. Both cases and controls were interviewed exactly in the same fashion, and except for the items in the questionnaire referring to the clinical aspects of

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the current medical condition, they both answered the same number and type of questions.

When the field staff found that a case had died or had become too ill to participate, he/she would ask to conduct the interview with a next of kin, preferably with the spouse, but children and other relatives were also considered apropppriate surrogate respondents. When a surrogate respondent had to be used for a case, a surrogate respondent was also used for the control. For instance, when the spouse of a case was interviewed in lieu of the case, we would seek to interview the spouse of the person selected as a control, even if the latter was available and willing to be interviewed. In this respect we should then note that cases and controls were matched in addition to SEX , AGE , SMOKING HISTORY and RESIDENCE, on the TYPE OF INTERVIEW conducted.

8 HISTOLOGY REVIEW.

An independent review of the pathology specimens initially examined to make the diagnosis of lung cancer seemed important for two reasons. First, to make sure that all cases were confirmed primary lung cancer cases, and second, to provide a uniform criteria of diagnosis. The procedure for such review was as follows.

The field staff would contact the pathology department of the

diagnosing hospitals and would request the slides or tissue blocks for the patient in question. In all but five patients such request was successful. The specimens would then be sent to a Pathologist at Memorial Sloane Kettering Cancer Center in New York City, who would review them blindly with regard to smoking history, the initial hospital diagnosis, and other risk factors. The review pathologist assigned each case a histological diagnosis according to the World Health Organization International Histological Classification of Tumours (86). The review diagnosis was then compared to the initial hospital diagnosis. If there was disagreement between initial and review diagnosis, a second pathologist from the same institution would review the slides and assign the final diagnosis. Even though a detailed histological classification was provided by the pathologists, for the purposes of these study we have used a coarse classification that divides our cases into the following histologic types: Epidermoid or squamous cell carcinoma, Small cell carcinoma, Adenocarcinoma, Large cell carcinoma, and Others.

9 EXPOSURE VARIABLES.

The main hypothesis of the study was concerned with the effects of passive smoking on lung cancer risk. In order to assess the magnitude of such an association, we needed to have both accurate measurements of exposure to the suspected risk factor and accurate measurement of the disease status. How the latter was achieved has

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been explained in the previous section dealing with histologic review. In this section it will be explained how the exposure to the risk factor was determined.

9.1 SPOUSE SMOKING HABITS.

Items 58 to 73 in the questionnaire (Appendix A) inquired about the smoking habits of up to four spouses per study subject. That information was used to create the following measurements of exposure: 1)Number of cigarettes smoked a day by the spouse(s). The number reported by the respondent was taken directly from the questionnaire if the case control had been married only once, or if only one of his/hers spouse(s) had smoked. If more than one marriage to a smoker was reported, the exposure was estimated to be the mean number of cigarettes/day smoked by as many spouses as reported (maximum 4). 2)Number of years the spouse smoked. This figure was taken directly from the reported number of years the first spouse smoked while married and living together with the study subject. When applicable -- that is, in the case of more than one marriage to a smoker -- the number of years smoked by subsequent spouses was simply added to the first figure. 3)Total number of cigarettes smoked by the spouse during married life. This variable was calculated by multypling the number of cigarettes smoked per day by 365 to obtain an estimate of the number of cigarettes smoked in a year; then, multiplying that figure by the number of years the spouse was reported to have smoked in the course of the marriage. When more than one spouse was reported as a smoker, the total married-life number of

cigarettes for each would be added into a single measurement of exposure.

9.2 EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD.

This variable was created with the information collected in the items marked with an asterisk in page 1/0 of Appendix A. Information about smoking in the household was collected for the 12 most recent residences in which the study subjects reported to have lived. It was calculated as follows: The number of years lived in each residence was multiplied by the number of smokers in that particular residence (inclusive of the spouse), and added over as many residences reported to have had smokers (maximum of 12). The resulting figure was expressed as the number of person/years of exposure experienced by the study subjects. It has to be emphasized that these units of exposure should not be confused with the conventional meaning usually attached to them in epidemiologic research. In this case these units are used to summarize the exposure of each individual according to intensity (number of smokers in the household) and duration (number of years living with smokers in the household) of such exposure. They do not indicate the collective experience of a group of individuals over a certain period of time.

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9.3 PASSIVE SMOKING IN THE WORKPLACE.

The information collected through the items marked with an asterisk in pages 168 and 169 of Appendix A was the basis on which to estimate exposure in the workplace. This variable was created in exactly the same manner as household exposure. That is, the number of years the study subject worked in a particular place was multiplied by the number of smokers who worked in the same room or area. This was done for the 12 most recent jobs and added over to obtain a single measurement of exposure. The units of exposure, as well as household exposure, are expressed in person/years; and their interpretation should also be similar: a summary of exposure for each study subject to smokers in the workplace over certain period of time.

9.4 PASSIVE SMOKING IN SOCIAL CIRCUMSTANCES.

Page No 173 in Appendix A shows the items asked during the interview in order to estimate exposure to secondary smoke in social circumstances. These items were intended to collect information on 3 aspects of exposure. The first is the type of social activities which are conducive to exposure to passive smoking; secondly, the frequency with which such activities were carried out; and thirdly, the stages in life (10 year intervals) in which such activities were carried out with that particular frequency. The information conveyed by these three aspects of exposure was summarized in a single index that goes

from zero to a maximum value of 96. This index is obtained by adding the information coded in items 186-200. For further details on the creation of the index of exposure the reader must refer to the Appendix. There, both the list of the activities included and the way in which the information was entered is self-explanatory.

10 POTENTIALLY CONFOUNDING VARIABLES.

Inspection of the data showed that cases and controls were different with regard to variables which were believed to affect lung cancer risk. It was decided that these should be considered in the analysis as potential confounders. We were aware, however, that the information available was not of uniform quality across variables. Whereas information on sociodemographic variables was likely to be highly reliable, the information pertaining to chemical and/or occupational exposures — all obtained on a self-reported basis — was not deemed so. Thus, we carried out the adjustment for confounding variables in two steps. The first, which we call "partial" adjustment, included only those variables for which we had "hard" information. Such variables were RELIGION (Catholic versus Other), INCOME, MARITAL STATUS (single versus other), and NUMBER OF CIGARETTES SMOKED/DAY among the former smokers. In the second step two other variables were added in order to carry out a "full" adjustment. These variables were: exposure to any of the CHEMICALS (never versus ever exposure) listed in items 202-218 in page 176 of Appendix A, and exposure to "FUMES, DUST OR RADIATION ON THE JOB" (see page 169 in

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Appendix A). In addition to these, other relevant variables were considered for inclusion, but a closer examination of their distribution among cases and controls showed no significant differences. These variables were: EXPOSURE TO DIESEL OR EXHAUST FUMES FROM BUSES, TRUCKS OR EQUIPMENT ; EXPOSURE TO A GAS COOKING RANGE AT HOME; EXPOSURE TO KEROSENE HEATERS; and EXPOSURE TO A COAL OR WOOD STOVE (pages 169 and 171 of Appendix A).

We believe that our best adjusted estimates were those obtained by the inclusion of the first group of variables, since they are based on the most reliable information. In the next chapter, therefore, we only present (in addition to the crude estimates) the results of the so-called "partial" adjustment.

11 ANALYSIS

The choice of statistical analysis techniques was primarily determined by the design of the study. The latter called for the use of techniques capable of accounting for the matching, as well as for techniques capable of dealing with complex situations in which covariates — in addition to the exposure variables — could be taken simultaneously into consideration.

Before explaining more fully how these techniques were applied, it is pertinent to mention that simpler techniques were also used to first explore the characteristics of the data collected. Univariate

statistics and/or simple frequencies were obtained for almost all of the variables for which we had information. Such exploration of the data also included — when apropriate — the use of stem and leaf or box-plot diagrams to determine the nature of the distribution of the variables, in both cases and controls. The comparability of these two groups also needed to be established and several statistical tests were performed to such an end. In the case of the variables that had been used to perform the matching (AGE, SEX, SMOKING HISTORY, RESIDENCE AND TYPE OF INTERVIEW), we knew of course that no differences were to be found. But there was no certainty that cases and controls would be equal in other respects. Sociodemographic variables such as number of years of school attendance, income, ethnic group, country of origin, number of times married, and others, were compared using either paired t-tests (continuous variables) or chi-square tests (McNemar's test for dicothomous variables or chi-square for categorical variables with more than two levels). In the same fashion those variables that were viewed as potential confounders were compared first before deciding whether or not to include them as confounders in the final analysis. When applicable, the comparison of the potentially confounding variables was done by treating the variables as both categorical (for example, yes/no exposure to gas cooking) and continuous (for example, number of years of exposure to gas cooking). Thus, the decision to include a variable as confounder was followed by the decision on whether to include it as a categorical or as a continuous variable. Logistic regression was used to determine if there was evidence to assume linearity on the effect of the potential confounder. It may be useful to advance now that none

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of the potentially confounding continuous variables (with the exception of income) showed indication of linearity. Therefore they were included only as categorical variables.

11.1 LOGISTIC REGRESSION FOR MATCHED CASE-CONTROL STUDIES.

Holford et. al. (87) have published a method to analyze pairwise matched studies based on the linear logistic model described by Cornfield et. al. (88). As pointed out by the authors, this method shows several features that make it the best available choice to analyze data sets such as the present one. First, it allows us to obtain the estimate of effect for one or more exposure variables while controlling for variables not considered in the matching. Second, it can provide estimates of the effect associated with different levels of one or more categorical exposure variables, as well as the estimates of effect for the levels (one unit change) of one or more continuous exposure variables. And third, it allows us easily to obtain estimates associated with the different levels of the matching variables.

In this adaptation of the logistic model the regressor variables are represented by the case-control differences of the value for the exposure (or confounding) variables, the intercept is not included, and the response is always positive (that is, for each value of the regressor variable there is always one case and one control). The resulting estimates are the maximum conditional likelihood estimates

of the parameters.

In the present analysis I used the program for logistic regression available in GLIM (89). The analysis of each of the exposure variables proceeded very much in the same way. The following, therefore, is a general description of the steps followed to assess the effect of each of these exposure variables on the risk of lung cancer.

11.2 EXPOSURE AS CATEGORICAL VARIABLES.

All information on exposure was collected in such a way as to allow the creation of variables that would reflect such exposure in a continuous scale. We considered it useful, however, to look first at the effect of the exposure variables as ordinal categories. For that matter all variables were transformed into new categorical variables. The cut-off points for the categories were chosen by following convention (e.g. packs of cigarettes/day) or by referring to what other authors have used in their studies (e.g. Trichopoulous categorization of exposure to cigarettes in a lifetime). Once the categories had been created and the information summarized in tables, the analysis proceeded in this way:

1) The model that assumes no association between risk factor and disease was fitted to the data. This is also referred to as the model with no parameters or the model of total symmetry.

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2) The logistic model that considers exposure as an ordinal categorical variable was fitted to the data. These models provided estimates of the effect of each of the levels of exposure using zero exposure as the reference category.

3) In order to test for a linear trend in the levels of the category, a third model was fitted. This included as the regressor variable the case-control differences of the mid-points of the category intervals. The estimate obtained represents the slope of the fitted line.

4) In order to test for the significance of the overall effect of the exposure variable, the model obtained in 2 was compared to the model obtained in 1. The resulting difference in G^2 tests the null hypotheses that all parameters in model 2 are zero, or equivalently, it tests whether model.2 provides a better fit to the data than the model of no association.

5) In order to test for the significance of the linear trend, model 3 was compared to model 1.

6) The statistical significance of the parameter estimates obtained in 2 and 3 was assessed by comparing each estimate to its standard error (Wald's tests not shown), or by estimating their 95% confidence intervals.

7) Violation of the assumption of the consistency of the odds ratios was checked by looking at the value of G^2 obtained in model 2 (Test of Quasy symmetry). The assumption of the consistency of the odds ratios is made under the adaptation of the logistic model used for the analysis of matched studies.

8) In the one case that the linear trend was found to be significant (exposure to passive smoking in the household), the next higher order model was fitted to the data. The quadratic term was represented by the case-control differences of the squares of the mid-points of the category intervals.

9) A last regressor variable was entered to compare the risk associated with zero exposure to the risk associated with any level of exposure (none versus some exposure). None of these models showed any significance and since they provide only a "coarse" assessment of exposure, they are not presented in the results.

11.3 EXPOSURE AS A CONTINUOUS VARIABLE.

The next step in the analysis was to treat the exposure variables as a continuum. It was believed that such an approach could detect significant effects not uncovered by the analysis of the exposure as

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categories. At this point it was also considered pertinent to look at estimates for specific strata of the study population. Previous studies have suggested that the effect of passive smoking may vary between the sexes, or by type of interview or according to smoking history. The matched design would not allow us to obtain estimates for the main effects of such variables (by design those effects have been set to be zero), but estimates for each of their levels could provide useful information on the relationship between the risk factor and the study disease. Also, previous research work has suggested that passive smoking may determine the type of histologic tumor developed by the patients. Therefore, we wanted to see if the magnitude or direction of the effect varied according to the histologic type considered.

In summary, the steps taken at this stage of the analysis were as follows.

1) A logistic model was fitted for each of the exposure variables. These models provided estimates of effect for the exposure in question, taking into account all 439 pairs available for analysis.

2) A logistic model was fitted for each of the exposure variables and their interaction with the variable TYPE OF INTERVIEW. From these models estimates for effects were obtained for SELF-RESPONDENTS and for SURROGATE RESPONDENTS.

3) A logistic model was fitted for each of the exposure variables and their interaction with the variable SMOKING HISTORY. From these models separate estimates were obtained for NEVER SMOKERS and FORMER SMOKERS.

4) A logistic model was fitted for each of the exposure variables and their interactions with the variable SEX. These models provided estimates for FEMALES and MALES.

5) A logistic model was fitted for each of the exposure variables and their interactions with the variable HISTOLOGIC TYPE. Separate effects were obtained for EPIDERMOID AND SMALL CELL CARCINOMA and ADENOCARCINOMA AND OTHERS.

6) Tests of the significance of the effects of all of the above parameters were obtained, as well as tests of the significance of the interactions. The latter are equivalent to testing the null hypothesis that the effect does not vary according to the levels of the stratifying variable.

7) More complex models including the exposure variable in question and two, three and four two-way interactions were fitted.

8) Models with the exposure variables and all the possible combinations of three-way interactions were fitted.

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9) Models obtained in 8 and 9 were compared to each other as well as to the simplest models obtained in 1 through 5.

10) The variables selected as potential confounders were included in the models obtained in 1 through 5.

11) A single model that contained the three mutually exclusive exposure variables (household, workplace and social exposure) and the confounders was fitted to the data.

12) A model was fitted to the data that contained only the two variables with significant effects and the confounders.

CHAPTER THREE

RESULTS

This chapter is divided into three sections. The first is devoted to the description of the study sample in terms of socio-demographic characteristics. In addition, it checks the distribution of the variables used to match cases to controls and presents the distribution of cases regarding histologic diagnoses. The second section examines the distribution of certain variables not taken into account by the matching process — variables which, by their nature, may be considered as potential confounders of the association between passive smoking and lung cancer (for example, pipe and cigar smoking). The third and last section is subdivided into four subsections, each one reporting the assessment of the association between lung cancer and a different measurement of exposure to passive smoking.

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1 DESCRIPTION OF THE STUDY SAMPLE AND DISTRIBUTION OF THE MATCHING VARIABLES.

The results presented here are based on the statistical analysis performed on data pertaining to 439 case-control pairs. Table No 1 presents the most relevant demographic characteristics of the study subjects. By design (i.e. matching), the sex distribution was set to be approximately even. Thus, there are 218 (49.7%) female case-control pairs and 221 (50.3%) pairs of males. In the same manner, age, which was matched within a + - five year age range, caused the mean age for the cases (67.05 years) to be very close to the mean age for controls (68.13 years). As is well known, most lung cancer patients acquire the disease later in life. This is likely to be a reflection either of a long latency period or of the requirement of a prolonged exposure to etiologic factors necessary for the development of the disease). Moreover, 77% of our case control-pairs reported themselves 60 years or older at the time of diagnosis. By the time the interview was conducted, an additional 3.0 % were reported to fall into that category. The latter increase was obviously due to the time elapsed between the discharge diagnosis, the obtaining of consent from the attending physician, the contacting of the patient him- or herself and, finally, the arrangement and conducting of the interview. Since survival among lung cancer cases is known to be poor, and since obtaining the information directly from the patient before death was considered crucial for the quality of the data sought, we tried to keep the lapse between diagnosis and interview as short as possible. As a consequence, the mean number of days that transpired between the

two events was 147 days. This allowed us to conduct direct interviews with 296 of the patients (67.0% of the total). As explained in the preceding section, cases and controls were also matched on type of interview, so that the same proportion of direct interviews applies to the control group.

One hundred and ninety seven pairs (45%) were comprised by never smokers and 242 (55%) by former smokers. As would be expected, most never smoking pairs were female (75.6%) and most smoking pairs were male (71.5%). The smoking history-sex distribution will be important when interpreting the results of the exposure variables. It must be remembered, therefore, that when presenting results for females we will be dealing mostly with non-smokers, and when presenting results for males we will be referring to a subgroup composed mainly of former smokers. Conversely, estimates for never smokers are based on more females than males, and estimates for former smokers on more males. In evaluating interactions we must also keep in mind that the estimates of effect for specific subgroups will be based on a varying number of pairs, and therefore will have different statistical power, depending on the particular interactions being evaluated. Thus, for instance, the estimates for never smoking males, will be calculated using smaller number of subjects than the estimate for former smoking males.

Over 90% of both cases and controls were whites. Blacks constituted 3.6% of the cases and 2.7% of the controls. No information on ethnic group was available in about 1% of cases and

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controls. Most patients reported themselves as having been born in the United States (88%). In addition to this country, 22 other countries, mostly European, were mentioned as place of birth. None of the differences in the distribution of ethnic group or national origin were statistically significant.

Fewer cases than controls reported ever to having been married (87% versus 92%). Similarly, at the time of the interview, fewer cases (60%) were reported to be married than controls. While these differences were statistically significant (Chi-square = 11.46, 1 df) the number of times being married or the mean number of years duration of marriage were not. Significant differences of religion were offered by the presence of more Catholics (54%) among the cases than among the controls (42.0 %), and by more Protestants among the controls (38%) than among the cases (32%) (Chi-square = 13.67, 4 df). Income was found to be significantly higher for the cases than for the controls. This finding suggests that matching on county of residence does not seem effective to control for economic status. However, another variable which is generally considered to be an indicator of socioeconomic status, i.e. number of years of school attendance, did not show any significant differences for cases and controls. The mean number of years of school attendance for cases was 11.44 years and, for controls, 12.7 years.

The distribution of histologic diagnoses resulting from the study review indicates that the majority of cases in our study were adenocarcinomas (222 cases, 50.6%); epidermoid carcinoma constituted

TABLE No. 1
RELEVANT CHARACTERISTICS OF THE STUDY POPULATION

	CASES	CONTROLS
SEX*		
FEMALES	49.7%	49.7%
MALES	50.3%	50.3
AGE*		
MEAN AGE IN YEARS	67.05	68.13
SMOKING HISTORY*		
NEVER SMOKERS	45.0%	45.0%
FORMER SMOKERS	55.0%	55.0%
TYPE OF INTERVIEW*		
SELF-RESPONDENTS	67.0%	67.0%
SURROGATE RESPONDENTS	33.0%	33.0%
ETHNIC GROUP		
NON-WHITE	2.7%	3.6%
WHITE	86.6%	85.6%
EDUCATION		
MEAN NUMBER OF YEARS OF SCHOOL ATTENDANCE	11.4	12.7
PLACE OF BIRTH		
UNITED STATES	89.7%	86.8%
OTHER	10.3%	13.2%
RELIGION		
CATHOLIC	54.0%	42.4%
OTHER OR NONE	46.0%	57.6%
HISTOLOGIC TYPE		
EPIDERMOID	50.6%	-
ADENOCARCINOMA	25.1%	-
LARGE CELL	10.3%	-
SMALL CELL	7.7%	-
OTHER	6.4%	-

* Matching variables

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

about one quarter of the patients (110 cases, 25.1%); large and small cell accounted for 45 (10.3%) and 34 (7.7%) cases. Finally, 28 patients were classified as "other" histologic types. We want to emphasize that this categorization of cases according to histologic diagnoses is based on the diagnoses provided by our study review, (except for the five cases in which the pathology slides could not be obtained). This distribution is very similar to the one derived from the initial hospital diagnoses. The overall agreement between the latter and our study review was 94.0%, with a Kappa value of 0.864.

2 DISTRIBUTION OF POTENTIALLY CONFOUNDING VARIABLES.

Some of the socio-demographic variables already described fall into the category of potentially confounding variables. Namely, marital status, income and religious affiliation. The magnitude and nature of the differences between cases and controls regarding these attributes have been pointed out, and the ways in which they have been taken into account in the analysis has been presented in the previous chapter. Other potentially confounding variables such as chemical, occupational, and residential exposures have been discussed in section 10 of the same chapter. Therefore, this section will concentrate on the non-matching variables not yet discussed. Of particular importance are those variables related to smoking habits. As explained in the previous section, the matching on smoking history was done on a dicothomous basis. That is, cases who were never smokers were matched to controls who never smoked, and cases who reported as having smoked

were matched with controls who were former smokers. This procedure, however, did not necessarily ensure that the particularities of the smoking habits of the former smokers -- such as intensity and duration of cigarette smoking -- were comparable among cases and controls. Nor did this procedure ensure that exposure to other forms of tobacco was similar in both groups. Thus, the exploration of the distribution of these variables seems in order.

The average number of years the ex-smoking cases reported having smoked was 29.9 years. This figure was not significantly different from the mean 28.3 years duration of the smoking habit reported by controls (paired t-test = 1.64 , p=.1024). However, the mean number of cigarettes per day smoked by the ex-smoking cases (28.9) was significantly higher than the mean daily number of cigarettes smoked by the controls (23.82) (paired t-test=3.74, p= .0002). This finding was recognized to be important for two reasons. First, it suggested that if an increased risk for lung cancer was found in the study, it might be due to the residual effect of past smoking habits, and not -- or not only -- due to exposure to passive smoking. Secondly, it made clear the need to control for this variable in the final analysis as a way to remove the potentially confounding effect, as well as to stress the need to obtain separate estimates of the effect of passive smoking for never and former smokers.

Exposure to other forms of tobacco did not show any significant difference between cases and controls. Both groups had about the same proportion of individuals who reported ever smoking cigars (78 cases

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

and 79 controls). The intensity of this habit was also similar for cases and controls (4.6 cigars/day for cases and 3.4 cigars /day for controls), as was the overall length of use (20.5 years for cases and 18.26 years for the controls). Cases and controls were also similar in proportion, intensity, and duration of pipe smoking. Eigthy three cases and 90 controls were ever pipe smokers. The cases smoked and average of 4.4 pipes a day during an average of 20.41 years. The controls smoked 4.6 pipes a day during an average of 19.9 years. The appropiate statistical test did not show significant differences for any of these variables. Only 3 cases and 1 control reported having smoked marijuana. This difference is not significant, and in any case the comparison is based on such small numbers as to have no meaningful interpretation or to raise concern regarding any effect on the results.

3 ASSESSMENT OF THE EFFECTS OF PASSIVE SMOKING ON LUNG CANCER RISKS.

In the following section the results of assessing the impact of passive smoking on lung cancer risk will be presented according to four different sources of exposure. These sources are: 1) smoking habits of the spouse(s), 2)smoking by all members of the household (inclusive of spouse), 3) smoking in the workplace, and 4) smoking that occurs in social circumstances.

3.1 SMOKING HABITS OF THE SPOUSE.

Most epidemiologic studies have chosen one measurement of spouse smoking as an indicator of exposure to passive smoking. In the present study the effect of spouse smoking as measured by three variables has been evaluated. The first variable considers the daily smoking habits of the spouse(s). The second concerns the number of years the spouse(s) sustained that particular smoking pattern. And the third variable — in fact a combination of the first two — reflects the total number of cigarettes smoked by the spouse(s) while married and living together.

3.1.1 ASSESSMENT OF THE EFFECT OF NUMBER OF CIGARETTES/DAY SMOKED BY THE SPOUSE.

Table No 2 presents the estimates of the effect of the spouse's daily smoking habits when analyzed as an ordinal categorical variable. In order to present results easily compared with those of other studies, each category reflects the standard number of cigarettes corresponding to a different number of packs of cigarettes/day. A logistic regression model was fitted to the data using the differences in exposure between cases and controls as regressor variables (See Statistical Analysis in the Methods Chapter). Through this technique, comparisons have been made between the risk associated with exposure to each of the categories of spouse daily smoking and the referent category represented by zero exposure. Table

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No 2 presents the estimates, standard errors, odds ratios and confidence limits for each of these comparisons. The highest risks observed correspond to odds ratios of 2.86 (for exposure to spouse smoking of more than 80 cig/day) and 1.23 (for exposure corresponding to 41 to 60 cigarettes/day). The corresponding confidence limits, however, indicate that these values are not significantly different from the null value. Unexpectedly, three of the estimates in the table suggest a decrease in risk for lung cancer for those exposed to 1-20 cigarettes/day (OR=.7897), to 21-40 cigarettes/day (OR=.9063), and to 60 to 80 cigarettes/day (OR=.4196). Likewise, these estimates are not statistically different from the null value, as shown in the same table.

A plot of the five log odds corresponding to each category is shown in Figure No 1 (estimates represented by diamonds at midpoint of category values). Four of the points suggest a possible linear relationship. In order to test for linearity in the categories, the case-control differences of the mid-points of each category were entered as the regressor variables in the logistic model. The estimate obtained for the slope of the fitted line (estimate=.001032, Wald test=.2271) was not statistically different from zero, therefore concluding that there is no evidence to support a linear response for the categories.

When compared to a model of total symmetry (G^2 = 10.29, 11 df) — that is, to a model with no parameters, that assumes no differences in exposure for cases and controls — neither the model for exposure as categories (G^2 = 5.304, 6 df), nor the model for linear trend (G^2 = 10.24, 10 df), seemed to provide a better fit to the data (ΔG^2 = 4.99, 5 df, and ΔG^2 = .05, 1 df, respectively). Along the same lines, a logistic model that compares zero exposure to any exposure (=> 1 cig/day) showed neither any significant effect nor any appropiate fit to the data, when compared to the model with no parameters (ΔG^2 = 2.72, 2 df).

The analysis of the effect of number of cigarettes/ day smoked by the spouse also included treating the exposure as a continuum. For that purpose a linear logistic model was fitted to the data. The odds ratio associated with the spouse smoking 1 pack of cigarettes/ day was 1.011 (Table No. 3. Its 95% confidence limits (0.866 - 1.18) includes the null value and therefore provides no evidence of a significant association with the study disease. It may be pertinent to mention at this point that when logistic regression is applied to the analysis of continuous data, the estimate of effect obtained for a particular unit of exposure can be used to calculate the estimate associated with other levels of exposure. For instance, by multypling the estimate for 1 pack of cigarettes/day (0.010998) by 2, 3 or 4, we would obtain the estimates of effect associated with the spouse smoking the respective number of packs/day. In the same fashion, multiplying the standard error of 1 pack/day by the quantities cited above will yield the variation associated with the estimate at that level of exposure. It should be evident by the way in which these estimates are obtained that higher exposures will always be associated with larger estimates (as well as with greater variation) so that the statistical significance of the estimates does not vary according to

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level of exposure. In the present case, the estimates for 2, 3, and 4 packs cigarettes/day would all be not significantly different from the null value; their confidence intervals would include such a figure.

Figure No 1 shows the line that represents the relationship between exposure (cigarettes/day in the X axis) and risk of disease (log odds in the Y axis), according to the logistic model fitted to the data (continuous line). Again, the almost entirely flat line suggests a lack of dose response relationship. The two other lines represent two subgroups of the study population. The large dash line corresponds to self respondents, and the small dash line to surrogate respondents. Both of these lines would seem to suggest effects due to exposure that are not only greater than the effect for the group as a whole, but also that move in opposite directions from one another. However, neither is significantly different from the line that represents all subjects, nor are they significantly different from one another. Likewise, the estimates that describe these lines are not significantly different from the null value.

The lower part of Table No 3 (lines 4-9) and Figures No 2, 3, and 4, present for the study population estimates and fitted lines, respectively, according to SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS. The significance tests and confidence limits in the table show no significant effect of spouse daily smoking when examined separately for never smokers and former smokers, males and females, and epidermoid and adenocarcinoma histologic types. Moreover, the tests of interaction of the exposure variable with SMOKING HISTORY,

TABLE No. 2

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO FIVE CATEGORIES OF CIGARETTES PER DAY SMOKED BY THE SPOUSE(S).

CIGARETTES /DAY	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 20	-.2361	.1558	.7897	.6819	1.0717
21 - 40	-.0984	.2032	.9063	.6086	1.3497
41 - 60	.2081.	.3390	1.2313	.6336	2.3930
61 -80	-.8684	.8751	.4196	.0755	2.3322
80 +	1.0500	1.1590	2.8576	.2947	27.7058

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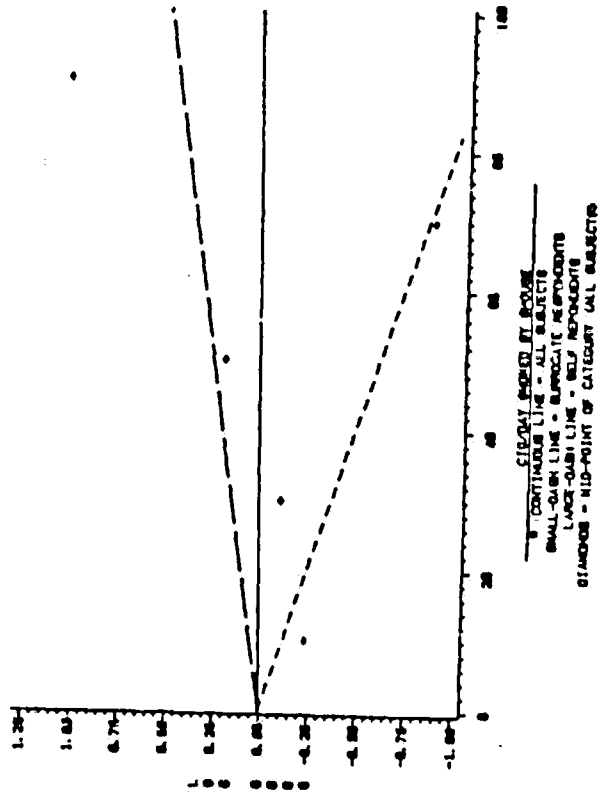
TABLE No 3

UNADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO
SPOUSE SMOKING OF 20 CIGARETTES/DAY.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.010998	.07928	1.0111	.8655	1.1810
SELF RESPONDENTS	.1072	.0940	1.1132	.9258	1.3384
SURROGATE RESPONDENTS	-.2402	.1543	.7865	.5812	1.0642
NEVER SMOKERS	-.0614	.1302	.9499	.7359	1.2262
FORMER SMOKERS	.0656	.1040	1.0571	.8622	1.2962
FEMALES	-.0230	.1059	.9773	.7941	1.2028
MALES	.05444	.1200	1.0560	.8347	1.3358
EPIDERMOID SMALL CELL	.1157	.1378	1.1227	.8570	1.4707
ADENOCA. & OTHERS	-.0420	.0980	.9589	.7913	1.1619

FIGURE No. 1

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



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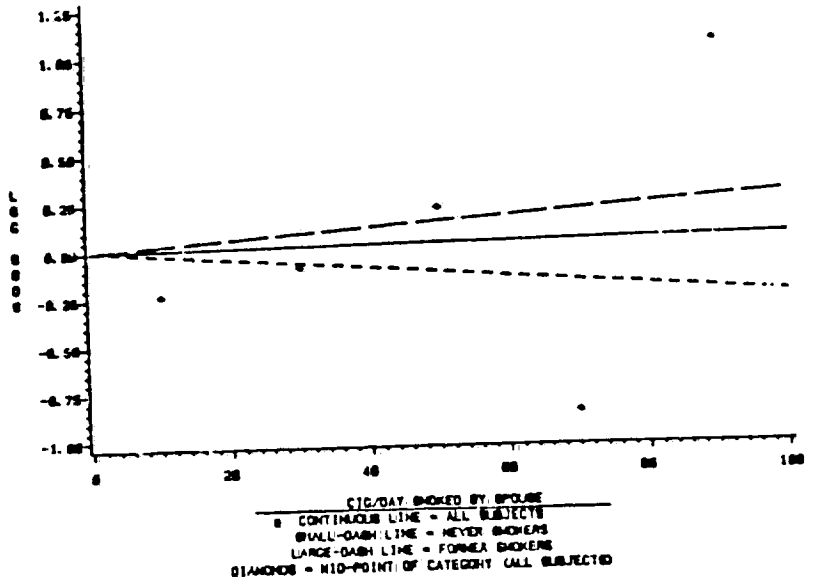
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 2

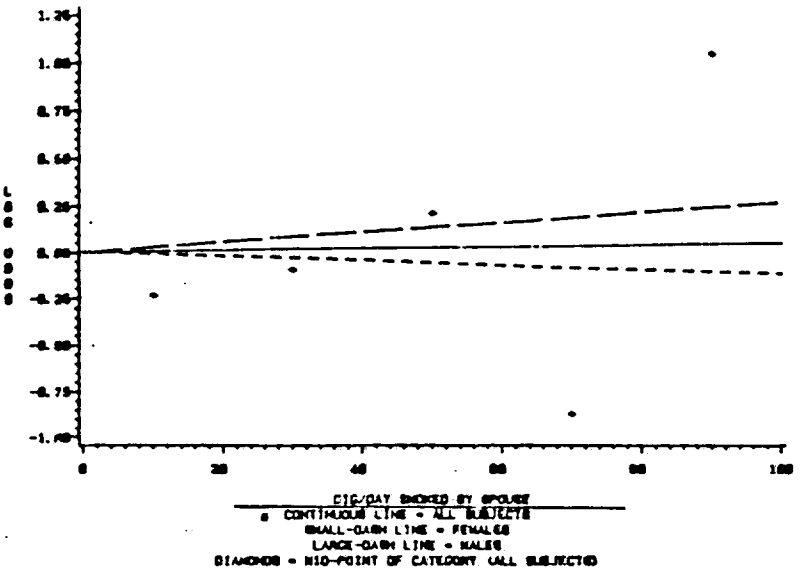
CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 3

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

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FIGURE No. 4

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES PER DAY SMOKED BY THE SPOUSE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

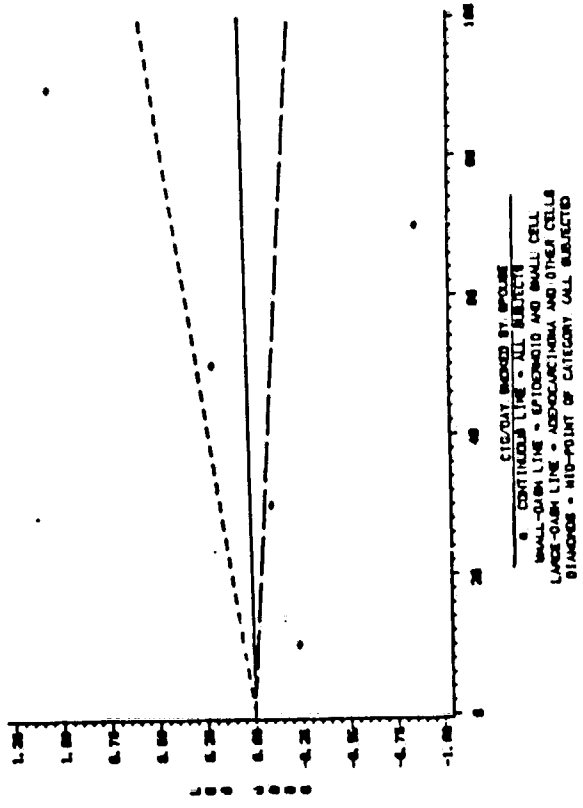

TABLE No. 4

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 20 CIGARETTES/DAY.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0152	.0831	.9849	.8369	1.1591
SELF RESPONDENTS	.0838	.0987	1.0874	.8962	1.3196
SURROGATE RESPONDENTS	-.2684	.1588	.7646	.5601	1.0437
NEVER SMOKERS	-.0684	.1271	.9338	.7279	1.1981
FORMER SMOKERS	.0247	.1101	1.02501	.8261	1.2718
FEMALES	-.0597	.1107	.9421	.7583	1.1703
MALES	.0454	.1274	1.0444	.8136	1.3407
EPIDERMOID/ SMALL CELL	-.0813	.1837	.9219	.6431	1.3215
ADENOCA. & OTHERS	-.0491	.1181	.9521	.7554	1.2001

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

SEX, AND HISTOLOGIC DIAGNOSIS are not significant, indicating that the estimates for the two subgroups in each of these stratifying variables are not significantly different from one another.

Table No 4 presents estimates for ALL SUBJECTS and for each level of the variables TYPE OF INTERVIEW, SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS obtained with the logistic regression model that includes confounding variables. A comparison of these values with those presented in Table No 3 shows no meaningful differences. The tests of significance support the previous conclusion of no significant association between exposure and study disease. There is also no evidence of differences in the lines representing the different subgroups for which the effect of exposure is being evaluated.

3.1.2 NUMBER OF YEARS OF SPOUSE SMOKING.

The assessment of years of exposure to spouse smoking as an ordinal categorical variable did not show evidence of a significant association with the study disease (Table No 5) All of the six estimates are accompanied by test results that are not statistically significant, as well as by confidence limits that include the null value. A plot of the estimates in Figure No. 5 (diamonds in mid-point of categories) did not suggest a strong dose-response relationship either. The absence of such relationship was confirmed by a non-significant test for the regressor variable representing a linear trend for the categories (estimate= -.00193, Wald= -.4552).

When number of years of spouse smoking was assessed as a continuous variable (Table No.6) it was found that 10 years of spouse smoking was associated with an odds ratio of 0.99 (95% CL: 0.912 - 1.074). Exposure to as much as 50 years of spouse smoking, roughly the highest exposure observed in these data, would decrease the odds ratio to 0.95 (95% CL: .6200 - 1.4600); but again, this is not statistically different than the risk for the non-exposed. Also in Table No 6 and in Figures No. 6 - 8, the estimates and fitted lines for the different levels of the matching variables and the two histologic types are presented. As shown, the point estimates for each of these subgroups fluctuates between positive and negative values, which in no case present evidence of being significantly different from the null value. Likewise, the estimates are not significantly different between levels of the variables SEX, SMOKING HISTORY and HISTOLOGIC DIAGNOSES, as evaluated by the interaction with the exposure variable. However, the interaction between the latter and TYPE OF INTERVIEW was found to be significant (Wald test= 2.13 > 1.96, $p < .05$), suggesting that the estimate for surrogate respondents is different from that for self-respondents. Nevertheless, as mentioned above, neither can be considered to be significant.

The inclusion of confounding variables in the logistic model generated the estimates presented in Table No 7. An inspection of these figures, for all subjects and by levels of the stratifying variables, supports the conclusion conveyed by the unadjusted estimates that there is no association with the study disease. Although this basic conclusion is not changed, it should be noted that

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TABLE No. 5

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO SIX CATEGORIES OF NUMBER OF YEARS SMOKED BY THE SPOUSE(S).

NUMBER OF YEARS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 10	-.0970	.2252	.9076	.5837	1.4112
11 - 20	-.3879	.2595	.6785	.4080	1.1283
21 - 30	-.2036	.2167	.8158	.5335	1.2475
31 - 40	.2061	.2158	1.2276	.8042	1.8740
41 - 50	-.2926	.2687	.7463	.4403	1.2637
50 +	-.5052	.8587	.6034	.1659	2.1943

TABLE No.6

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 10 YEARS

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0100	.0417	.9900	.9123	1.0744
SELF RESPONDENTS	.0526	.0510	1.0540	.9537	1.1648
SURROGATE RESPONDENTS	-.1423	.0754	.8674	.7483	1.0054
NEVER SMOKERS	-.0336	.0633	.9670	.8541	1.0948
FORMER SMOKERS	.0082	.0560	1.0082	.9034	1.1252
FEMALES	.0020	.0610	1.0020	.8892	1.1292
MALES	-.0207	.0520	.9798	.8846	1.0847
EPIDERMOID/ SMALL CELL	.04017	.0653	1.0410	.9159	1.1832
ADENOCA. & OTHERS	-.0450	.0545	.9560	.8592	1.0638

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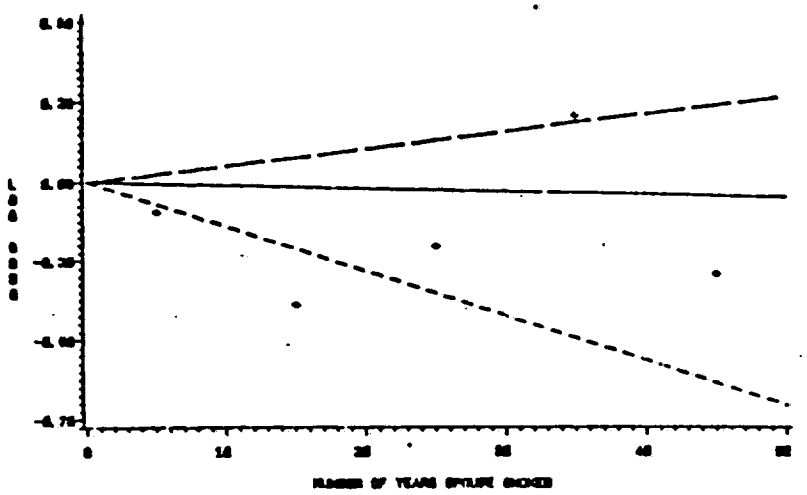
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No 5

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS[a], SELF RESPONDENTS[b], AND SURROGATE RESPONDENTS[b]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]

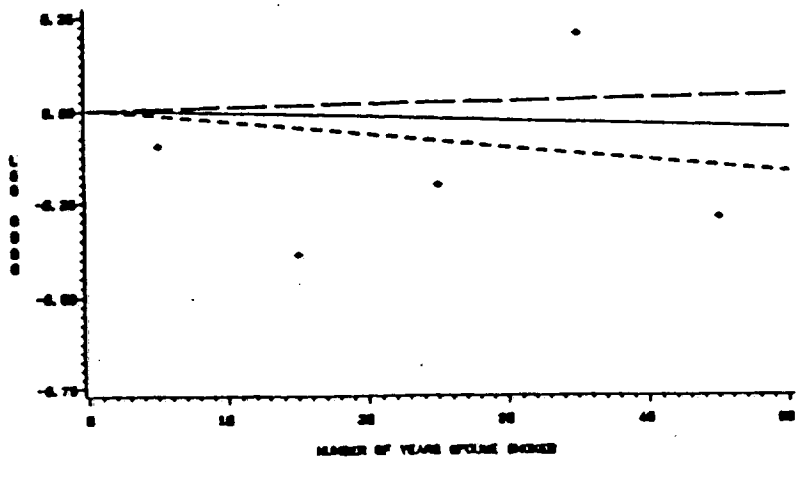


NUMBER OF YEARS SPOUSE SMOKED

[a] CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No 6

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS[a], NEVER SMOKERS[b], AND FORMER SMOKERS[b]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]



NUMBER OF YEARS SPOUSE SMOKED

[a] CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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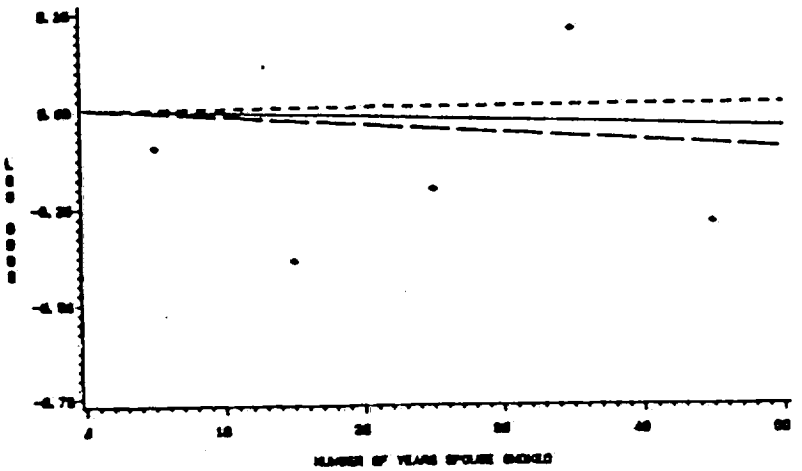
FIGURE No. 7

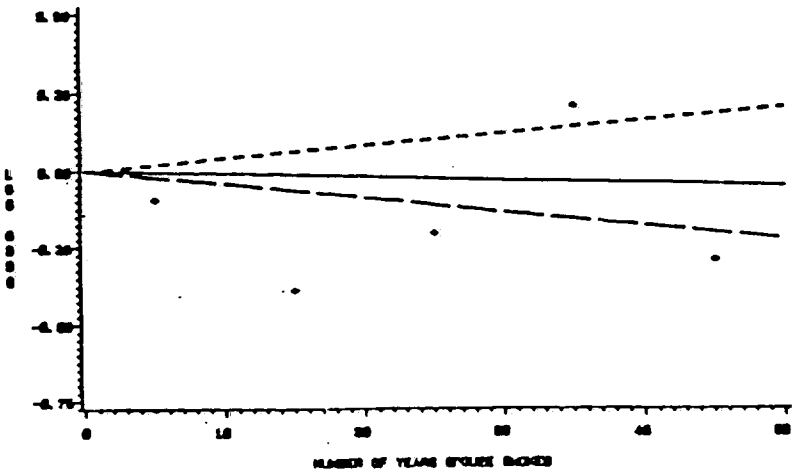
CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 8

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF YEARS THE SPOUSE SMOKED; FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

TABLE No 7

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO
SPOUSE SMOKING OF 10 YEARS

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0106	.0441	.9894	.9075	1.0788
SELF RESPONDENTS	.0481	.0538	1.0493	.9442	1.1661
SURROGATE RESPONDENTS	-.1325	.0789	.8759	.7504	1.0224
NEVER SMOKERS	-.0330	.0657	.9675	.8507	1.1004
FORMER SMOKERS	.0075	.0590	1.0075	.8976	1.1310
FEMALES	-.0049	.0633	.9951	.8789	1.1266
MALES	-.0158	.0608	.9843	.8736	1.1089
EPIDERMOID/ SMALL CELL	-.1151	.0951	.8913	.7397	1.0739
ADENOCA. & OTHERS	-.0617	.0604	.9402	.8351	1.0584

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the inclusion of confounding variables causes a change in the sign of the estimates for females and for epidermoid tumor type. This change, however, is not accompanied by a change in the test of significance.

3.1.3 TOTAL NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE.

Although already described in the previous chapter, it is important once again to emphasize at this point the manner in which the total number of cigarettes smoked by the subject spouse(s) during married life was calculated: the number of cigarettes smoked per day was multiplied by 365 to obtain the total number of cigarettes smoked in a year. This amount was then multiplied by the number of years of marriage or the number of years of cohabitation. If there was more than one spouse, the figures for each were added up into a single total measurement of exposure. The resulting figures can be numbers on the order of the hundreds of thousands. This may surprise the reader of this report, however, it must be mentioned that these seemingly high numbers do not in fact represent unusual exposures. For instance, a subject married during 35 years to a smoker of 1 pack of cigarettes per day would be exposed to over 250,000 cigarettes over the course of his/her married life (20 cigarettes/day X 365 days X 35 years).

The total number of cigarettes smoked by the spouse was first evaluated as a categorical variable. The categories used were chosen to be identical to those used by Trichopoulos in his study of Greek

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

women. The estimates of the effects for the 5 categories assessed are presented in Table No 8. The first four estimates, corresponding to exposures of up to 400,000 cigarettes, show a negative sign, suggesting that the effects may be contrary to the hypothesized. Viewed statistically, however, these values are not significantly different from the null value, as demonstrated by the confidence intervals also presented in Table No 8. The fifth estimate, corresponding to an exposure of more than 400,000 cigarettes (OR = 1.046), suggests a small risk above the risk for the non-exposed. But again, this figure does not reach statistical significance (95% CL: .6532 - 1.6762). The plot that presents the estimates of effect for the five categories in a logarithmic scale (Figure No 9) suggests that a test of linear trend should be performed. The parameter representing this linear trend was found not to be significant. Comparing the logistic model for exposure as categories and the model for categories as a linear variable, with the null model of no parameters (i.e. total symmetry model), provided further evidence of no association between exposure and study disease. Neither one showed itself to fit the data better than the null model (ΔG^2 = 1.95, 5 df, and ΔG^2 = .0061, 1 df, respectively).

Exposure, assesed as a continuous variable through a logistic regression model, yielded an estimate of effect equivalent to an odds ratio of 1.0175 for exposure to 200,000 cigarettes during married life (Table No.9). This estimate was found not to be significant, and, as explained in a previous section, indicates that any estimate for higher or lower exposures based on the same logistic model will be

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TABLE No. 8

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO FIVE CATEGORIES OF TOTAL NUMBER OF CIGARETTES SMOKED BY THE SPOUSE(S) DURING MARRIED LIFE.

NUMBER OF CIGARETTES	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1-100,000	-.2029	.1696	.8163	.5630	1.1838
-200,000	-.1377	.2165	.8714	.5678	1.3372
-300,000	-.2130	.2358	.8082	.5091	1.2830
-400,000	-.0782	.3087	.9247	.5050	1.6935
400,000 +	.04535	.2404	1.046	.6532	1.6762

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

TABLE No. 9

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 200,000 CIGARETTES.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.0173	.0757	1.0175	.8772	1.1805
SELF RESPONDENTS	.0964	.0894	1.1012	.9242	1.3121
SURROGATE RESPONDENTS	-.2028	.1509	.8164	.6074	1.0973
NEVER SMOKERS	-.0157	.1189	.9844	.7798	1.2428
FORMER SMOKERS	.0399	.0894	1.0407	.8734	1.2400
FEMALES	.0207	.1000	1.021	.8393	1.2420
MALES	.1274	.1096	1.1359	.9163	1.4081
EPIDERMOID/ SMALL CELL	.0536	.1221	1.0551	.8306	1.3403
ADENOCA. & OTHERS	-.0055	.1096	.9946	.8023	1.2329

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FIGURE No. 9

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

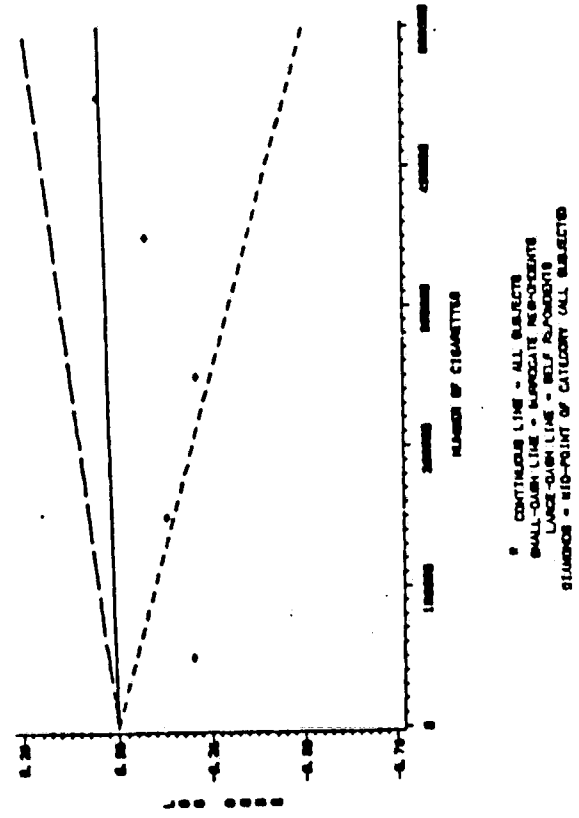
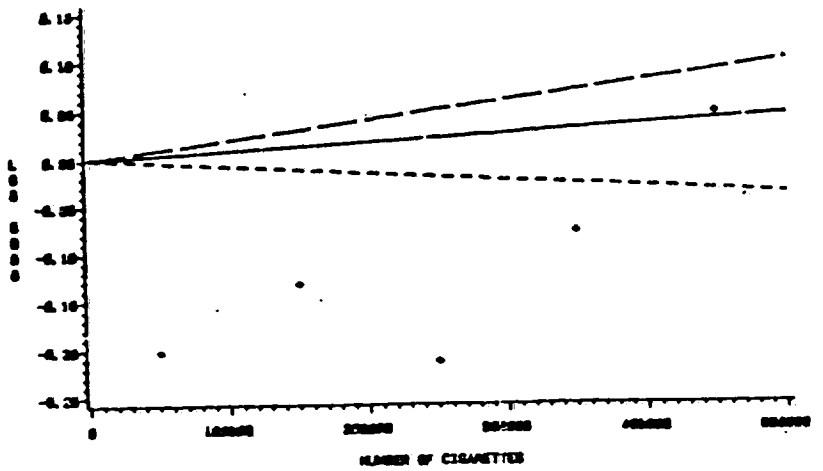


FIGURE No. 10

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

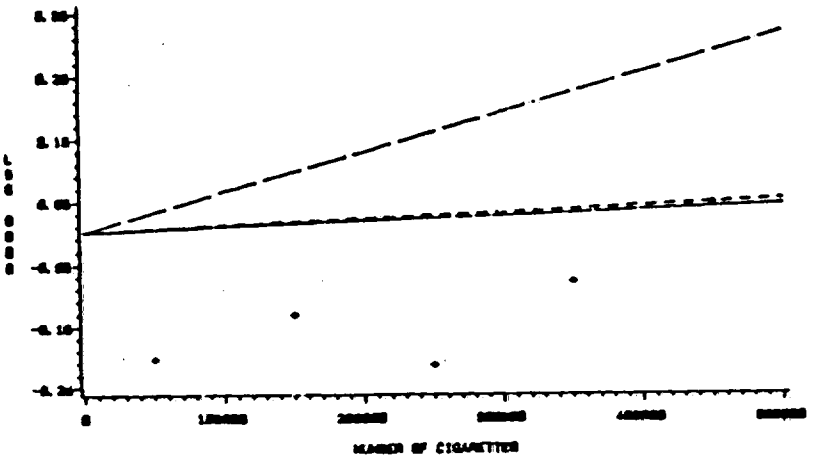


NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 11

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

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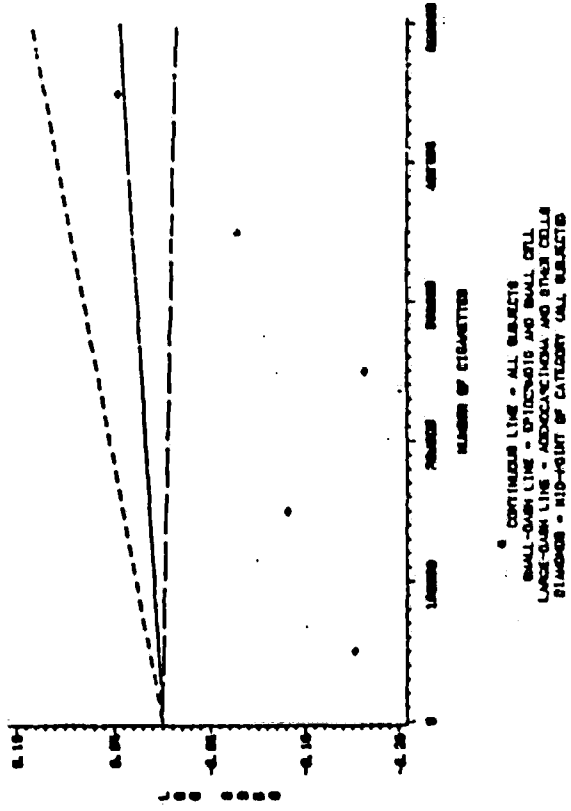
FIGURE No. 12

CHANGE IN LUNG CANCER LOG ODDS WITH NUMBER OF CIGARETTES SMOKED BY THE SPOUSE DURING MARRIED LIFE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



NUMBER OF CIGARETTES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY ALL SUBJECTS

TABLE No. 10

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE TO SPOUSE SMOKING OF 200,000 CIGARETTES.

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.0128	.0804	1.0129	.8652	1.1858
SELF RESPONDENTS	.0886	.0694	1.0926	.9170	1.3019
SURROGATE RESPONDENTS	-.1897	.1557	.8272	.6097	1.1224
NEVER SMOKERS	-.0212	.1226	.9790	.7699	1.2450
FORMER SMOKERS	.0382	.2460	1.0390	.6428	1.6793
FEMALES	.0067	.1048	1.0067	.8202	1.2357
MALES	.0218	.2190	1.0218	.6652	1.5696
EPIDERMOID/ SMALL CELL	-.1776	.1759	.8372	.5931	1.1818
ADENOCA. & OTHERS	-.0828	.2366	.9205	.5790	1.4636

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

equally non significant. Also in Table No. 9 estimates for the levels of the stratifyung variables TYPE OF INTERVIEW, SMOKING HISTORY, SEX and HISTOLOGIC DIAGNOSIS do not show significant effects , and in all cases the estimates were not found to be significantly different within levels of the same variable. In-addition to this each of the models that included the interaction between the stratifying variables and the exposure variable did not provide better fit to the data than the models for all subjects, or than the model of total symmetry. An illustration of the lines fitted for all subjects, along with the levels of the stratifying variables, is shown in Figures 9 trough 12.

Finally, the total number of cigarettes smoked during married life was assessed in the presence of confounding variables. Table No 10 shows the estimates obtained and their confidence limits. In no case did the presence of covariates in the model improve the fit to the data or unveil any significant effect of the exposure variable on lung cancer risks.

3.2 PASSIVE SMOKING IN THE HOUSEHOLD.

Cases and controls were questionned about the number of smokers with whom they shared their 12 most recent residences, together with the duration of each cohabitation. The number of smokers in each household, multiplied by the number of years lived in each particular household, and summed over the 12 residences, estimates the number of person/years of exposure to passive smoking.

Inspection of the raw data showed that for some of the 12 residences — particularly those corresponding to early stages in life — the information on the number of smokers in the household was missing. The data was analyzed in two ways, each making a different assumption about these missing values. Under the first assumption we assumed that one smoker had lived in the households for which information was missing if, that is, there was evidence that the study subject had lived in previous or future residences with at least one other smoker. Under assumption number two it was assumed that there was no exposure (i.e., no smokers in the household) for those residences in which information was missing. Results from analyzing the data under the two assumptions are practically identical. However, both sets of results will be presented to allow the reader to make his/her own conclusions regarding the handling of missing values.

3.2.1. RESULTS UNDER ASSUMPTION 1.

The results of analyzing household exposure as a categorical variable are shown in Table No. 11. Except for the estimate corresponding to 26-50 person/years of exposure (OR=.9154, 95% CL: .5510 - 1.5208), all point odds ratios suggest an increased risk of lung cancer associated with household exposure to passive smoking. However, only the highest exposure — which also produces the highest estimate of effect — shows evidence of statistical significance (OR for exposure to +175 person/years= 2.85 (95% CL: 1.09 - 7.42]). Still, the plot of the eight estimates presented in Figure No 13 suggests that a linear model may be adequate to describe the relationship between the categories of

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

exposure and the risk of disease. In the usual manner, a variable reflecting linearity in the levels of the categories (the case-control difference of the midpoints of the categories) was entered in the regression model. The resulting model showed to be significantly different from the model with no parameters (ΔG^2 = 9.01, 1 df). In addition, the estimate representing the slope for the fitted line was found to be significantly different from zero (estimate= .004485, Wald= 2.95). The comparison of the model for the categories with the model for the "linear" categories did not provide evidence of departure from linearity (ΔG^2 = 5.87, 7 df). A higher order model with a quadratic term was fitted to the data but it was found not to be significant.

The model fitted to the data to assess the effect of exposure as a continuous variable yielded estimates that support the existence of an association between exposure and study disease. The odds ratio associated with 150 person/years of exposure was 1.856, with lower (1.218) and upper (2.830) 95% confidence limits well above the null value (See Table No 12).

Using the same model we can estimate the odds ratio associated with a very high exposure of 250 person/years as varying between 1.389 and 5.66, as indicated by the point estimates confidence limits.

The effect of household smoking according to TYPE OF INTERVIEW does not show differences in the effect for self-respondents versus surrogate respondents (Table No 12). However, when SMOKING HISTORY is

considered, the effect for never smokers is not significant, whereas the effect for former smokers is. This finding is all the more puzzling because both estimates are almost identical in value and because the test of interaction suggests that they are not significantly different from each other. The effect for each of the two sexes is also estimated to be very close to one another. In this case, however, both are significant and not different from each other.

A higher effect of household passive smoking was found associated with epidermoid and small cell histologic types (OR=2.83) than for adenocarcinoma and other cell types (OR=1.42). Moreover, the effect for epidermoid type is significant (95% CL: 1.39-5.76), whereas the effect for adenocarcinoma is not (95% CL: .835 - 2.41). Figures No 13 - 16 illustrate the lines for the regression models for each of the subgroups described above.

The model that assesses the effect of household exposure in the presence of confounding variables yields results that are different from the results of the model without such variables (Table No 13). The estimate of effect for the whole group is slightly lower (OR = 1.556), but no change is observed in its statistical significance (95% CL = 1.0006 - 2.42). The estimates for surrogate respondents, self-respondents, former smokers, males, females, and epidermoid histologic type -- formerly significant -- do have confidence intervals (in the presence of covariates) that include the null value, and point estimates which suggest lesser effects than the unadjusted estimates. The point estimate for adenocarcinoma (OR=1.87), although still lower

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TABLE No. 11

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE HOUSEHOLD *

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	.1269	.2815	1.1353	.6539	1.9712
26 - 50	-.0884	.2590	.9154	.5510	1.5208
51 - 75	.4514	.2661	1.5705	.9322	2.6458
76 - 100	.4437	.2922	1.5585	.8790	2.7633
101 - 125	.2795	.3139	1.3225	.7148	2.4467
126 - 150	.5194	.4595	1.6810	.6830	4.1372
151 - 175	.5368	.4490	1.7105	.7095	4.1241
175 +	1.0460	.4887	2.8462	1.0922	7.4176

*Results under assumption 1. See text for details.

TABLE No. 12

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD *

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	0.6186	0.2151	1.8563	1.2178	2.8298
SELF RESPONDENTS	.5469	.2625	1.7279	1.0329	2.89041
SURROGATE RESPONDENTS	.7632	.3774	2.1451	1.0238	4.4947
NEVER SMOKERS	.61065	.3186	1.8416	.9863	3.4387
FORMER SMOKERS	.6252	.2918	1.8686	1.05482	3.3103
FEMALES	.6258	.3120	1.8697	1.0144	3.4464
MALES	.6120	.2970	1.8441	1.0303	3.3006
EPIDERMOID/ SMALL CELL	1.0395	.3626	2.8278	1.3894	5.7552
ADENOCA. & OTHERS	.34935	.2700	1.4182	.8354	2.4074

*Results under assumption 1. See text for details.

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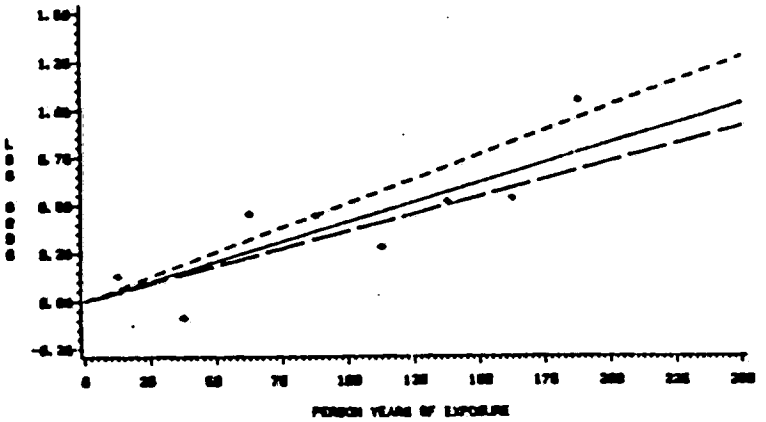
FIGURE No. 13

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, SELF RESPONDENTS *, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

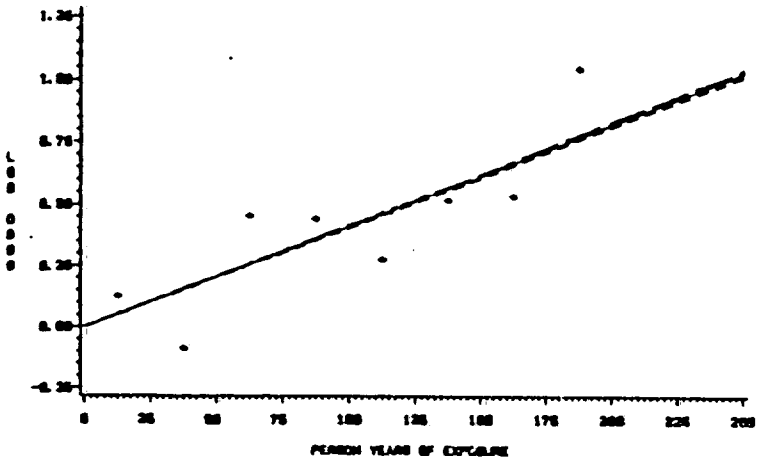


*Results under assumption 1. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 14

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD*, FOR ALL SUBJECTS*, NEVER SMOKERS *, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



*Results under assumption 1. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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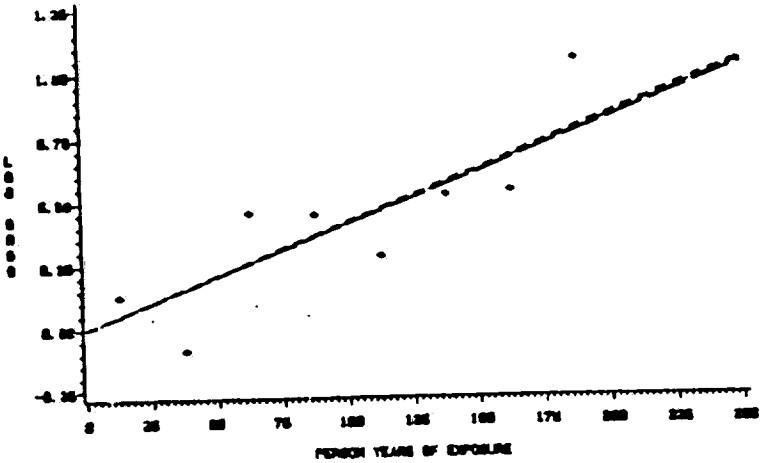
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 15

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE
TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[A],
FEMALES[@], AND MALES[@];
AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[@]

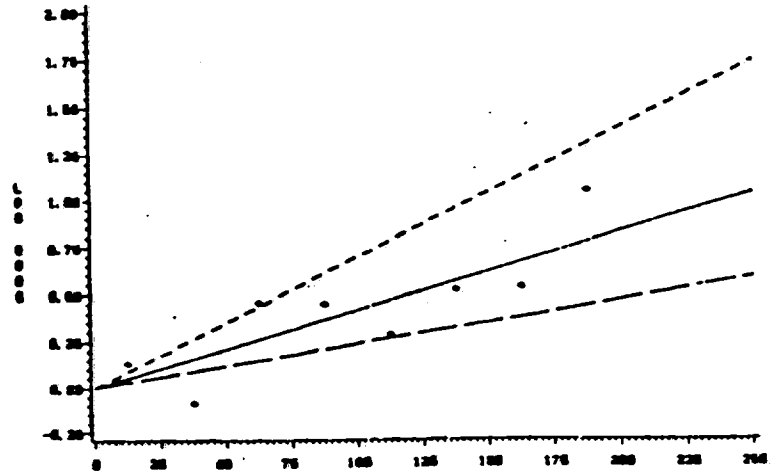


@Results under assumption 1. See text for details.

A CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 16

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE
TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[@],
EPIDERMOID/SMALL CELL[@], AND ADENOCARCINOMA/OTHER[@];
HISTOLOGIC TYPES
AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[@]



@Results under assumption 1. See text for details.

A CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

TABLE No. 13

ADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD ●

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.4422	.2253	1.5561	1.0006	2.4200
SELF RESPONDENTS	.3238	.2764	1.3824	.8041	2.3766
SURROGATE RESPONDENTS	.6726	.3937	1.9593	.9056	4.2391
NEVER SMOKERS	.3753	.3093	1.4554	.7938	2.6685
FORMER SMOKERS	.5157	.3266	1.6748	.8831	3.1764
FEMALES	.4239	.3256	1.5279	.770	2.8926
MALES	.4585	.3090	1.5817	.8631	2.8986
EPIDERMOID/ SMALL CELL	.8428	.5008	2.3230	.8704	6.1998
ADENOCA. & OTHERS	.6248	.3188	1.8678	1.0000	3.4886

●Results under assumption 1. See text for details.

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than the estimate for epidermoid type (OR=2.32), takes on a borderline significant value.

3.2.2 RESULTS UNDER ASSUMPTION 2.

Table No 14 presents the results of analyzing household exposure as a categorical variable when household exposure was calculated under assumption 2. Except for the first two estimates, all suggest an increased risk for lung cancer among the exposed. The plot of the estimates (Fig No 17) also seems to suggest that the risk increases with increasing exposure. While none of the estimates is significant (see confidence limits in the table), the linear trend is (ΔG^2 = 7.014, 1 df, going from the model with no parameters to the model with the regressor representing a linear trend for the categories). Thus, in comparison with the estimates obtained under assumption 1, the present estimates only differ in the non-significance of the estimate for the highest exposure. When analyzed as a continuous variable (Table No 15 the estimate of effect (OR= 1.73 for 150 person/years of exposure) is slightly lower than the effect obtained under assumption 1 (OR = 1.856). However, their confidence intervals overlap to a considerable degree (95% CL: 1.218 - 2.83 and 1.137 - 2.640. respectively). Significant effects were found for only two of the subgroups analyzed, former smokers (OR = 1.770 , 95% CL: 1.0008 - 3.132) and epidermoid histologic type (OR = 2.585, 95% CL: 301 - 5.137). Inclusion of confounding variables in the model (Table No 16) results in non-significant effects for these and the other subgroups, as well as for the group that comprises all subjects

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

TABLE No. 14

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE HOUSEHOLD*

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	-.0958	.2669	.9087	.5386	1.5332
26 - 50	-.2604	.2410	.7707	.4806	1.2361
51 - 75	.2884	.2478	1.3343	.8210	2.1686
76 - 100	.2451	.2839	1.2778	.7326	2.2290
101 - 125	.1030	.2972	1.1085	.6191	1.9848
126 - 150	.6191	.4547	1.8573	.7618	4.5291
151 - 175	.2093	.4513	1.2328	.5090	2.9857
175 +	.8521	.4849	2.3446	.9064	6.0648

*Results under assumption 2. See text for details

TABLE No. 15

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE HOUSEHOLD*

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.5492	.2146	1.7318	1.1371	2.6376
SELF RESPONDENTS	.5063	.2622	1.6592	.9924	2.7739
SURROGATE RESPONDENTS	.6356	.3754	1.8881	.9045	3.9410
NEVER SMOKERS	.5226	.3192	1.6864	.9021	3.1526
FORMER SMOKERS	.5712	.2910	1.7704	1.0008	3.1316
FEMALES	.5204	.3102	1.6826	.9181	3.0905
MALES	.5754	.2940	1.7778	.9982	3.1654
EPIDERMOID/ SMALL CELL	.9496	.3504	2.5848	1.3006	5.1368
ADENOCA. & OTHERS	.2802	.2775	1.3234	.7682	2.2798

*Results under assumption 2. See text for details

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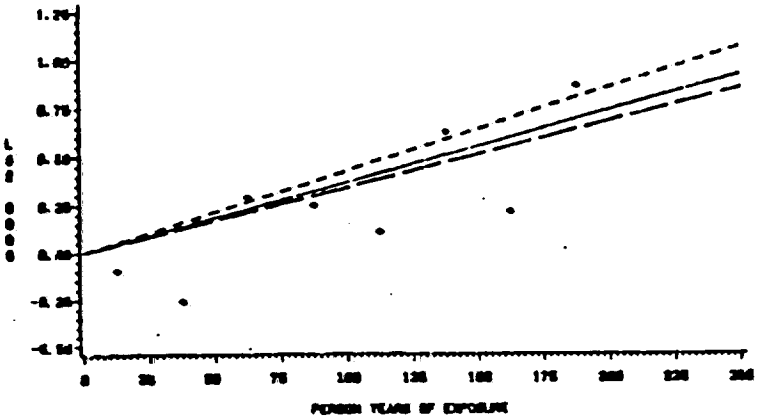
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 17

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[a], FOR ALL SUBJECTS[b], SELF RESPONDENTS[c], AND SURROGATE RESPONDENTS[d]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]

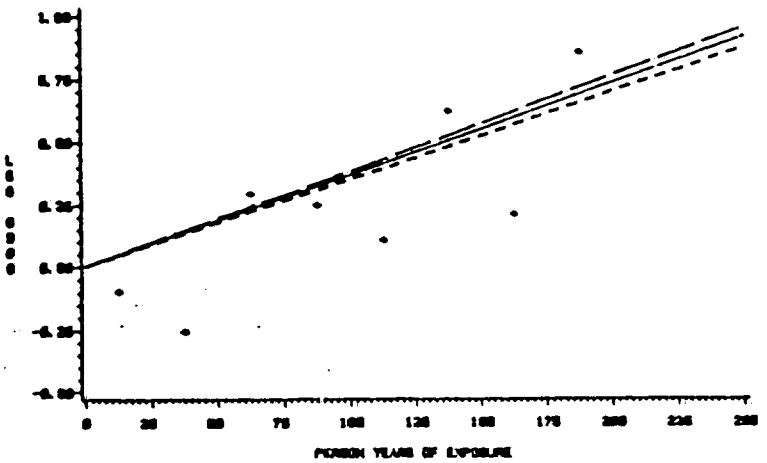


[a]Results under assumption 2. See text for details.

[b] CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 18

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[a], FOR ALL SUBJECTS[b], NEVER SMOKERS[c], AND FORMER SMOKERS[d]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]



[a]Results under assumption 2. See text for details.

CONTINUOUS LINE = ALL SUBJECTS
[b] SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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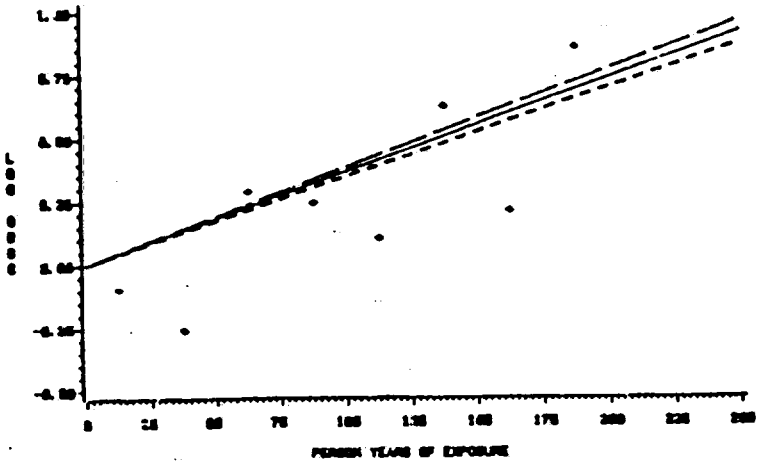
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 19

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[a], FEMALES[a], AND MALES[a]; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]

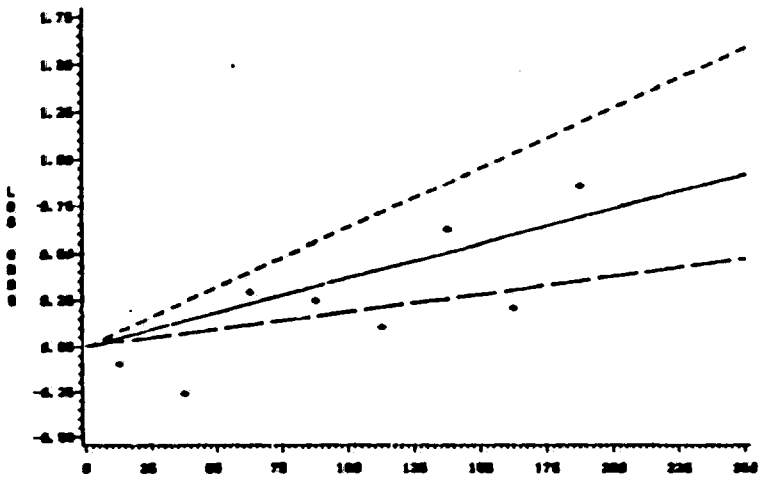


@Results under assumption 2. See text for details.

a CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 20

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE HOUSEHOLD[@], FOR ALL SUBJECTS[a], EPIDERMOID/SMALL CELL[a], AND ADENOCARCINOMA/OTHER[a]; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE[a]



a CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

@Results under assumption 2. See text for details.

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TABLE NO. 16

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
150 PERSON/YEARS SMOKING IN THE HOUSEHOLD @

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	.3732	.2252	1.4624	.9342	2.2580
SELF RESPONDENTS	.2818	.2763	1.3256	.7713	2.2782
SURROGATE RESPONDENTS	.5510	.3906	1.7349	.8068	3.7304
NEVER SMOKERS	.4332	.3256	1.5422	.8146	2.9197
FORMER SMOKERS	.3186	.3091	1.3752	.7503	2.5204
FEMALES	.3112	.3249	1.3651	.7240	2.5739
MALES	.4293	.3101	1.5362	.8365	2.8212
EPIDERMOID/ SMALL CELL	.7696	.4988	2.1590	.8123	5.7385
ADENOCA. & OTHERS	.5691	.3165	1.7667	.9500	3.2855

@Results under assumption 2. See text for details

(OR = 1.45, 95% CL: .934 - 2.258).

3.3 EXPOSURE TO SMOKING IN THE WORKPLACE.

Nine categories of smoking in the workplace were created according to different levels of exposure. The values included within each category (except for the referent zero exposure) are shown in Table No 17 under the heading PERSON/YEARS. The interpretation of such units has been explained in the previous chapter in the section that describes the exposure variables

Inspection of the estimates obtained showed effects ranging from odds ratios as low as 0.4664 to odds ratios above the null value (1.187, 1.186, 1.166). None of these is statistically significant (see columns for confidence limits in the table). When these estimates are plotted (Fig. No 21) their distribution in the figure is scattered, thus suggesting no dose-response relationship, the absence of which was confirmed by the non significance of the effect for the variable representing a linear trend for the categories (estimate= -.000287, Wald test= -.2839). Neither the model that assesses exposure as an ordinal categorical variable, nor the model that assesses the linear trend for the categories, provides a better fit to the data than the null model of no association (ΔG^2 = 7.83, 8 df, and ΔG^2 = .084, 1 df, respectively). This further denies evidence for an association between exposure to smoking in the workplace and lung cancer.

The assessment of exposure in the workplace as a continuous

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TABLE No. 17

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF SMOKING IN THE WORKPLACE

PERSON/YRS	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 25	-.2091	.2006	.8113	.5477	1.2019
26 - 50	.1705	.2513	1.1859	.7247	1.9407
51 - 75	.1536	.3083	1.1660	.6372	2.1337
76 - 100	-.6531	.4402	.5762	.2427	1.3630
101 - 125	.1717	.4548	1.1873	.4869	2.8954
126 - 150	-.3472	.4542	.7067	.2901	1.7212
151 - 175	-.7622	.5176	.4666	.1692	1.2870
175 +	-.0377	.2141	.9630	.6330	1.4652

TABLE No. 18

UNADJUSTED ESTIMATES, ODDS RATIOS, AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF 150 PERSON/YEARS SMOKING IN THE WORKPLACE

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0060	.0104	.9941	.9740	1.0145
SELF RESPONDENTS	.0138	.0170	1.0139	.9806	1.0483
SURROGATE RESPONDENTS	-.1108	.1249	.8951	.7008	1.1433
NEVER SMOKERS	-.05329	.0649	.9481	.8348	1.0767
FORMER SMOKERS	-.0047	.0105	.9953	.9751	1.0160
FEMALES	-.3140	.0817	.8691	.8257	1.1374
MALES	.0055	.0105	1.006	.9851	1.0265
EPIDERMOID SMALL CELL	-.0068	.0124	.9912	.9674	1.0156
ADENOCA. & OTHERS	.0037	.0223	1.0037	.9608	1.0484

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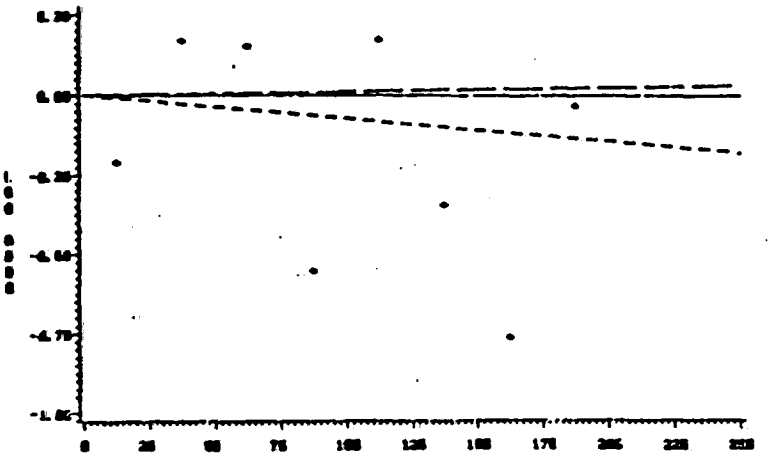
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No 21

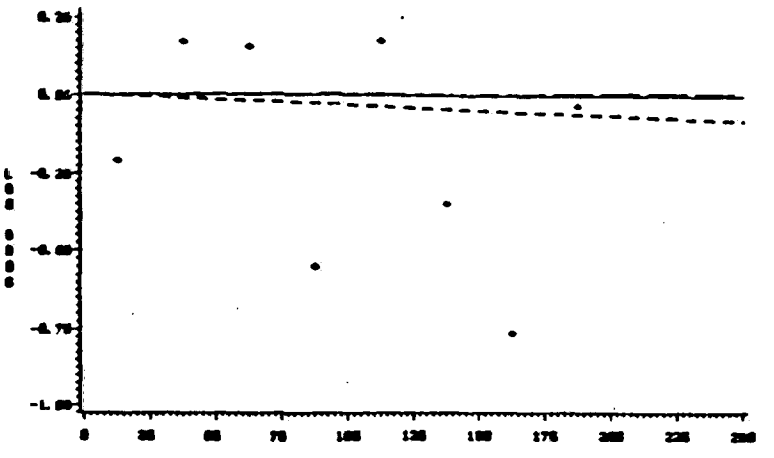
CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*, AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = SURROGATE RESPONDENTS
LARGE-DASH LINE = SELF RESPONDENTS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 22

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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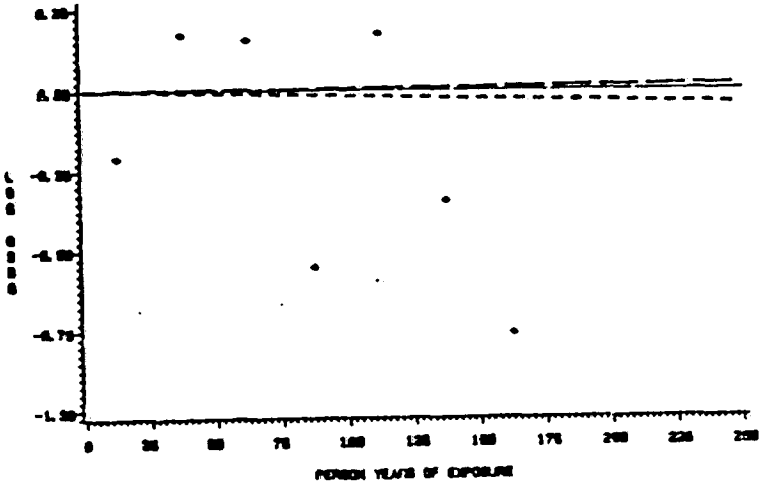
Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 23

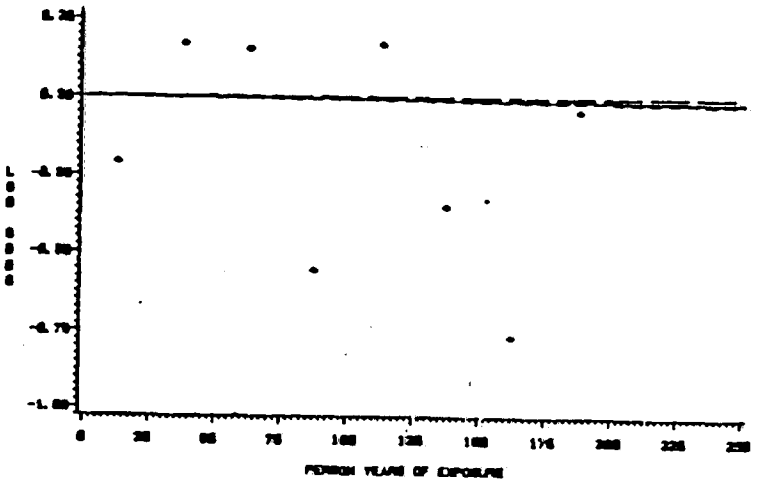
CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No 24

CHANGE IN LUNG CANCER LOG ODDS WITH PERSON/YEARS OF EXPOSURE TO PASSIVE SMOKING IN THE WORKPLACE, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*; HISTOLOGIC TYPES AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

TABLE No 19

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
150 PERSON/YEARS SMOKING IN THE WORKPLACE

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.0101	.0106	.9900	.9797	1.0107
SELF RESPONDENTS	.0105	.0170	1.0106	.9775	1.0446
SURROGATE RESPONDENTS	-.1447	.1345	.8653	.6648	1.1263
NEVER SMOKERS	-.0900	.06716	.9139	.8012	1.0425
FORMER SMOKERS	-.0081	.0104	.9919	.9719	1.0124
FEMALES	-.0541	.0657	.9473	.8009	1.1205
MALES	-.0094	.0105	.9906	.9704	1.0113
EPIDERMOID SMALL CELL	-.0154	.0222	.9847	.9430	1.0285
ADENOCA. & OTHERS	-.0115	0120	.9886	.9656	1.0121

variable supports the findings described for the categorical exposure variable. The odds ratio associated with an exposure of 150 person/years was 0.994, with lower (0.974) and upper (1.014) 95% confidence limits that include the null value (Table No. 18). Moreover, examination of the estimates for the different subgroups defined by the levels of the stratifying variables further support the lack of evidence for an association (lower part of Table No 18 and Figures No 21-24). Likewise, assessment of the effect of exposure obtained from models that include the confounding variables do not provide statistically significant estimates (Table No 19).

3.4 EXPOSURE TO PASSIVE SMOKING IN SOCIAL CIRCUMSTANCES.

Eight categories corresponding to different levels of exposure to passive smoking in social settings were compared to zero exposure through the fitting of a logistic model. Such a model provided a better fit to the data than the model with no parameters (ΔG^2 = 26.41, 8 df). The estimates for the two lowest exposures correspond to odds ratios of 1.838 and 1.064 (Table No. 20). The suggestion of increased risk for lung cancer for these categories of exposure, however, is not supported by the wide confidence limits that include the null value. The six remaining estimates of effect — all non significant — do take negative values; they also seem to indicate a strong linear trend in that direction. Figure No. 25 shows the points suggestive of such linear trend. A test provided the necessary statistical evidence (estimate = -.02263, Wald= - 4.380). In

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summary, by fitting a logistic model to the data that includes exposure as a categorical variable, we found two things: first, that the resulting model fits the data better than a model with no parameters (even though each parameter in the first model is not significantly different from zero), and second, that when categories are made to represent increasing doses of exposure, they show a linear trend opposite to that hypothesized, that is, a decrease in risk with increasing exposure.

The analysis of the index of social exposure to passive smoking as a continuous variable does not change the picture (Table No. 21). Exposure to 20 units of the index of social exposure is accompanied by an odds ratio of 0.699 (95% Confidence limits: 0.5202 - .7850). The estimates for the different levels of the stratifying variables are all close to the value cited above, with confidence limits equally exclusive of the null value. Each of these are shown in the lower part of Table No 21, and the lines representing the linear trends appear in Figures 25 through 28.

Furthermore, the inclusion of confounding variables in the models fitted have very little impact on the values of the point estimates (Table No. 22). The similarity of adjusted and unadjusted estimates is also reflected in overlapping confidence intervals. In two instances, however, the introduction of confounding variables had the effect of yielding non-significant estimates. For surrogate respondents the confidence limits around the odds ratio (0.957) include the null value (0.6424 - 1.426), in the same way as do the confidence limits for the

TABLE No. 20

ESTIMATES, ODDS RATIOS AND 95% CONFIDENCE LIMITS FOR EXPOSURE TO EIGHT CATEGORIES OF PASSIVE SMOKING IN SOCIAL SITUATIONS

EXPOSURE INDEX	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
1 - 10	.6087	.8638	1.8380	.3381	9.9916
11 - 20	.0617	.8644	1.0637	.1954	5.7889
21 - 30	-.1034	.8497	.9018	.1705	4.7684
31 - 40	-.4946	.8538	.6098	.1144	3.2606
41 - 50	-.5363	.8635	.5849	.1077	3.1777
51 - 60	-.5000	.8657	.6065	.1112	3.3094
61 - 70	-1.4440	.9571	.2360	.0362	1.5402
70 +	-1.8700	1.4550	.1541	.0089	2.6693

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TABLE No. 21

UNADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
20 UNITS IN THE INDEX OF EXPOSURE TO SOCIAL PASSIVE SMOKING

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.4478	.1060	.5390	.5202	.7850
SELF RESPONDENTS	-.4614	.1240	.6367	.4993	.8119
SURROGATE RESPONDENTS	-.4386	.1945	.6449	.4405	.9442
NEVER SMOKERS	-.5628	.1591	.5696	.4170	.7781
FORMER SMOKERS	-.3510	.1420	.7040	.5329	.9300
FEMALES	-.8692	.1674	.5121	.3689	.7110
MALES	-.2798	.1380	.7559	.5768	.9907
EPIDERMOID/ SMALL CELL	-.3604	.1786	.6974	.4914	.9898
ADENOCA. & OTHERS	-.4926	.1300	.6110	.4736	.7884

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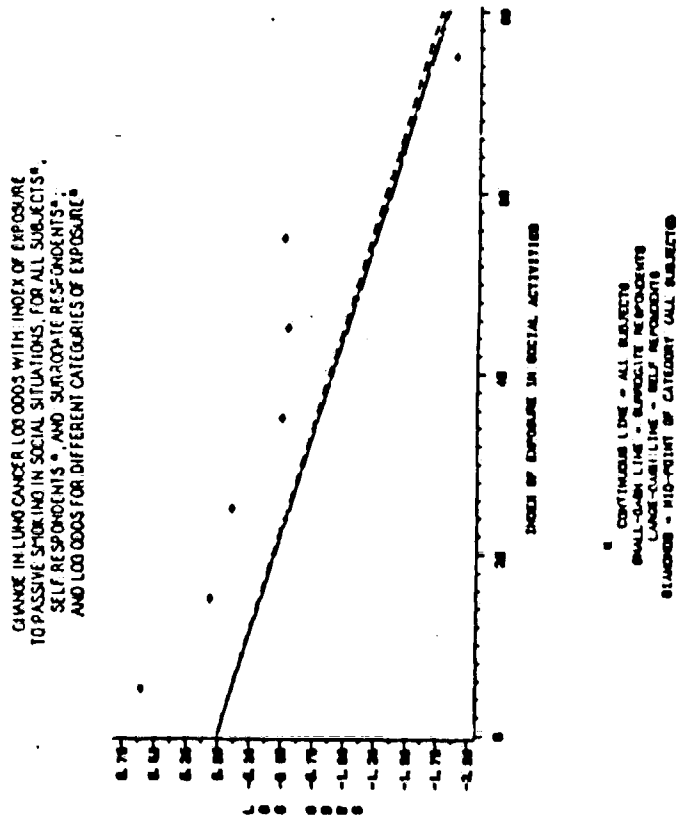


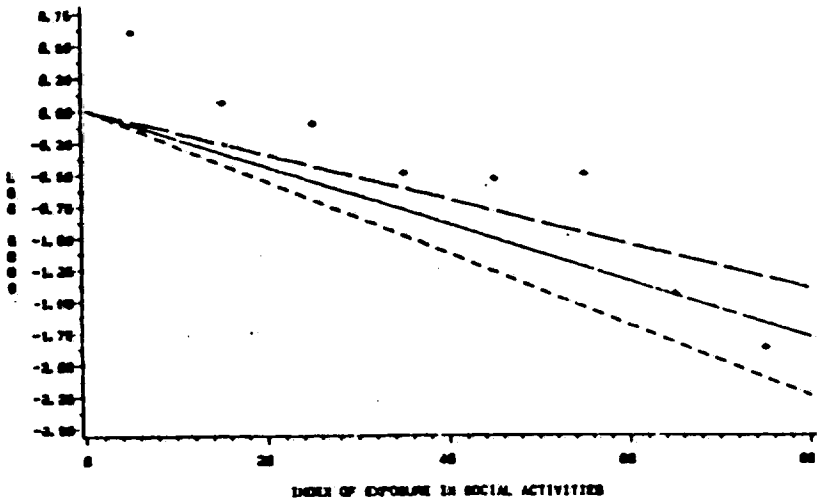
FIGURE No. 25

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, SELF RESPONDENTS*, AND SURROGATE RESPONDENTS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

FIGURE No. 26

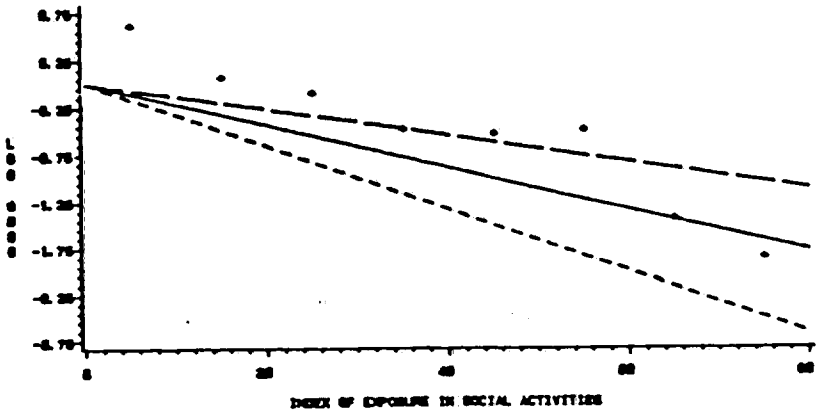
CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, NEVER SMOKERS*, AND FORMER SMOKERS*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = NEVER SMOKERS
LARGE-DASH LINE = FORMER SMOKERS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

FIGURE No. 27

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, FEMALES*, AND MALES*; AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = FEMALES
LARGE-DASH LINE = MALES
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

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Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

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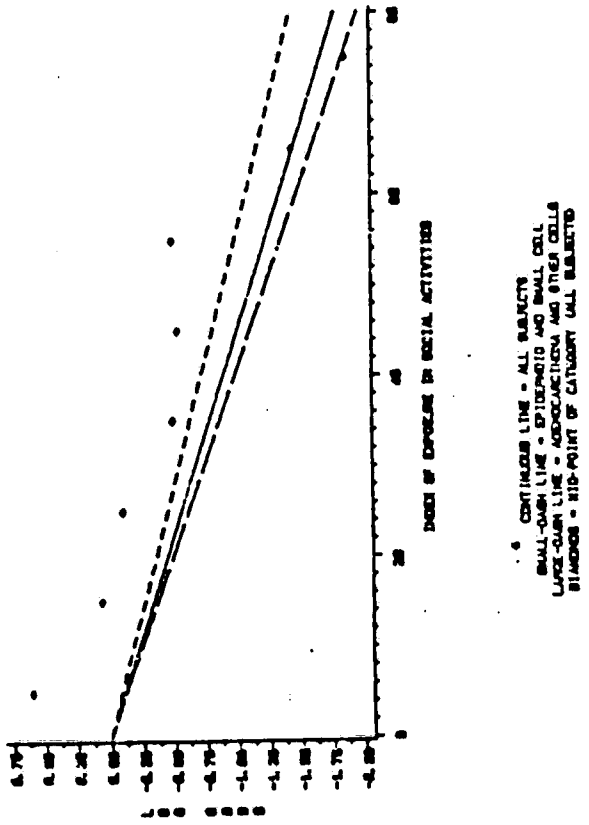
FIGURE No. 26

CHANGE IN LUNG CANCER LOG ODDS WITH INDEX OF EXPOSURE TO PASSIVE SMOKING IN SOCIAL SITUATIONS, FOR ALL SUBJECTS*, EPIDERMOID/SMALL CELL*, AND ADENOCARCINOMA/OTHER*, HISTOLOGIC TYPES

AND LOG ODDS FOR DIFFERENT CATEGORIES OF EXPOSURE*



INDEX OF EXPOSURE TO SOCIAL ACTIVITIES

* CONTINUOUS LINE = ALL SUBJECTS
SMALL-DASH LINE = EPIDERMOID AND SMALL CELL
LARGE-DASH LINE = ADENOCARCINOMA AND OTHER CELLS
DIAMONDS = MID-POINT OF CATEGORY (ALL SUBJECTS)

TABLE No. 22

ADJUSTED ESTIMATES, ODDS RATIOS,
AND CONFIDENCE LIMITS FOR A DIFFERENTIAL OF EXPOSURE OF
20 UNITS IN THE INDEX OF EXPOSURE TO SOCIAL PASSIVE SMOKING

GROUP	ESTIMATE	STANDARD ERROR	ODDS RATIO	95% LCL	95% UCL
ALL SUBJECTS	-.4694	.1107	.6254	.5034	.7769
SELF RESPONDENTS	-.4816	.1305	.6178	.4783	.7979
SURROGATE RESPONDENTS	-.0439	.2034	.9571	.6424	1.4259
NEVER SMOKERS	-.5310	.1626	.5880	.4275	.8086
FORMER SMOKERS	-.4141	.1512	.6609	.4914	.8890
FEMALES	-.6806	.1714	.5063	.3619	.7084
MALES	-.2990	.1485	.7416	.5544	.9923
EPIDERMOID/ SMALL CELL	-.3020	.2418	.7393	.4603	1.1876
ADENOCA. & OTHERS	-.3963	.1443	.6728	.5070	.8928

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

estimate for epidermoid histologic type does (OR = .7393, 95% Confidence limits: 0.4603 - 1.188).

CHAPTER FOUR

DISCUSSION

The hypothesis that lung cancer may be etiologically associated with exposure to environmental tobacco smoke has only recently received attention from epidemiologists and other scientists. The possibility of such an association had been raised in the early 1970's, but it was not until this decade that the first population studies addressing this issue were published. The scientific and, above all, the political ramifications of the subject seemed to demand quick answers. It is not surprising, then, that some of the first reports did not come from studies specifically designed to evaluate the purported association. They were the result of cleverly analyzed information that had been collected for other purposes. These studies were very valuable in throwing some light on the degree of the suspected association, but also they suffered from methodologic drawbacks that cast some doubt on the reliability of their results. Later studies have provided further and more specific information.

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However, the complex nature of the problem, along with the imperfection of present research tools, have precluded the establishment of definite conclusions. As it is almost always the case in epidemiologic research, it is the information from many different studies that will provide the evidence necessary either to reject or to accept the existence of the association. The present study was carried out to further assess the relationship between passive smoking and lung cancer, as well as to provide answers to some of the methodological problems encountered by other authors. In this chapter I will present a discussion of the general aspects of the study that may have had an effect on our results, such as sample size, composition of our study population (i.e. inclusion of both sexes, inclusion of former smokers, etc.), approach to data collection, choice of statistical techniques, and so on. This will be followed by a more specific discussion of the results of each of our exposure variables, focusing on the way in which these results compare with others previously reported.

The present study is to date the largest ever conducted on this subject. The implication of this fact reflects on the improved statistical power of our study over other studies with regard to their ability to detect differences in risk between the exposed and the unexposed. When the estimate of effect is expected to be moderate or small, as has been the case as suggested by previous epidemiologic and laboratory studies, consideration of sample size takes on special importance. Our estimation of sample size required to detect an effect of the order reported independently by Hirayama and Trichopoulous

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resulted in a figure of 450 case-control pairs, given that a matched design would be used. We were able to assemble 439 pairs that met the eligibility criteria fully. A sample of this size provides a a close to 95% probability of correctly rejecting the null hypothesis (power calculation based on an odds ratio of 2.0; proportion of exposed controls to spouse smoking, p, of 0.25; and significance level, α, of

It has been suggested that the estimates found by Hirayama and Trichopoulous are too high, in light of what is known about smoke uptake by non-smokers (the uptake has been estimated to be equivalent to the smoking of 0.1 to 1.0 cigarette per day [65]). It follows that the use of such estimates would overestimate the power of any given sample size. An odds ratio of 1.3 is believed to reflect more accurately the risk associated with the level of exposure attained by passive smoking (65). When we use the latter estimate to calculate the statistical power of our sample size, the resulting figure is still higher than the conventionally accepted 80%. Furthermore, when in these calculations we change the value of the proportion of the exposed controls from 0.25 to 0.50 (the proportion of exposed controls actually observed in our study), our statistical power increases above 90%.

The difficulty in gathering a large enough number of cases for study derives from the fact that most lung cancer cases occur among smokers. Even though the latter are probably exposed to large amounts of environmental tobacco smoke as a consequence of both their own smoking and their association with other smokers, they are unsuited

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

for a study of the effects of passive smoking, since their own habits would tend to mask any effect due to environmental smoke. We recognized that the ideal group to be studied was a group of never smokers. It became evident, however, that the population we were working with would not yield enough never smoking cases in any practical period of time. Instead of reducing our sample size at the expense of statistical power, it was decided to include ex-smokers in the study. The major prospective studies (90-91) have shown that the risk of lung cancer among former smokers can decrease, after 15 to 20 years, to a point where it resembles the risk of the never smokers. On the average the ex-smokers included in our sample had quit 18 years prior to their participation in the study. We were aware, nonetheless, that some residual effect of past smoking habits might still show in our data and thus confound the effect due to passive smoking.

We took three steps to ensure that our conclusions would not be affected by the inclusion of former smokers. These are: 1) the design of the study established that cases and controls should be matched on the basis of smoking history, 2) separate estimates of effect were obtained for smokers and former smokers, and 3) we controlled in the analysis for a variable that represented the number of cigarettes the ex-smokers used to smoke per day. Our results provided evidence that the inclusion of former smokers was not inappropiate. In no case did we find differences in the estimates of effect between never and former smokers which were statistically significant. Nevertheless, a residual effect due to past smoking habits was found. Former smokers

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of 1 pack of cigarrettes/day showed a statistically significant odds ratio of 1.38. It should be emphesized that this effect was controlled for in the analysis (as explained in number 3, above) and therefore is not to be viewed as responsible for any effect found for passive smoking.

Most researchers have restricted their studies on passive smoking exclusively to women. This is again related to the fact that it is easier to find non-smoking lung cancer cases among women than among men. In this choice it is implied to a certain extent that results can then be extrapolated to men. That is, it is assumed that men are as susceptible to environmental smoke as women, although this is not as easily observed in a male population because men acquire lung cancer as a consequence of their own smoking. While this proposition makes sense, we felt that it deserved to be evaluated. The finding of an association in males would strengthen the evidence of the carcinogenic effect of environmental smoke. Our study includes also the largest series of male non-smoking lung cancer cases (28.5% of these are never smokers and 71.5% are former smokers).

Our cases were drawn from all diagnostic and treatment facilities operating in the study area. Further checks for cases were performed at the New York State Tumor Registry. Except for a few cases who may have left the area in order to get medical care in other regions, we are confident of having detected all incident cases occurring during the study period. Our response rate of 76% can be considered good for most conventional standards. We do not have detailed information on

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the characteristics of the individuals who refused to participate, but it is the impression of the field research assistants that the reasons for refusal were more of a medical nature — i.e. the case was too ill to participate — rather than associated with any particular sociodemographic characteristics.

Correct classification of the study subjects according to their smoking history is crucial in studies on passive smoking. Inclusion of current smokers would spuriously increase the risk for the study disease. When smoking status of the reported cases was ascertained as part of determining elegibility for participation in our study, only those reported in the medical records as former smokers, never smokers or of unknown smoking status were contacted by telephone to further confirm their smoking histories . In addition to this, the research assistant would at the time of the interview further question these subjects in this regard . The need to confirm the smoking history stated in medical records is best illustrated by Garfinkel's findings (30). In that study close to 40% of the women with lung cancer classified as non-smokers (or smoking status not stated) on the hospital records, had been smokers at some time. In our study no attempt was made to confirm the smoking history of those reported as smokers, or even to establish contact with them. It seems less likely, however, that a former or a never smoker would report him/herself as a current smoker, thus escaping inclusion into the study.

The close scrutiny of our cases and controls regarding their

smoking histories strongly indicates that misclassification was not a likely event. Previous studies have been questioned in this regard. The relatively high lung cancer mortality among non-smoking women as compared to smoking women in Hirayama's study (25), as well as the high mortality for other tobacco-related diseases, have suggested that some smoking women may have reported themselves to belong to the non-smoking group. This would not be surprising in a traditional society such as Japan. The consequences of such misclassification would be to overestimate the effect due to passive smoking.

The Greek study (27) can also be criticized on the same grounds. The claim that more than 75% (40 out of 51) of lung cancer cases were diagnosed among non-smoking women is inconsistent with the proportion reported in the literature. It is considered that only about 10% of all lung cancer in women ocurrs in non-smokers (the corresponding figure for men is 2.0%). It is therefore likely that this study confounded the effect of passive smoking with the effect due to direct cigarette smoking, at least to a certain degree.

Before our study, only Garfinkel and coworkers (30) had carried out an independent review of the histologic diagnoses of cases. In most other reports the authors had relied on the discharge diagnoses recorded in the patient's medical records. The degree to which those diagnoses were based on examination of pathology specimens is varied. In Trichopoulous' study only 35% had an histologic diagnosis (27). The corresponding figure for Akiba's study is 57% (32). Pelayo Correa reports 97% (29). Both Hirayama's work and Garfinkel's first study

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using the American Cancer Society data relied exclusively on death certificates (24-25). The importance of histologic diagnoses is that it provides the most accurate measurement of disease status. Inclusion of other cancers can bias the results either away from or towards the null value, depending on whether or not they are related to smoking. The latter is the most likely situation since inclusion of other cancers would tend to be random. An additional advantage of obtaining the histologic diagnosis is that it allows us to estimate the effect for specific histologic types. This is of particular importance to uncover any specificity that would strenghten the evidence of a causal relationship. We were able to obtain almost a 100% of histologic confirmation, and given the excellent agreement between our reviewer and the initial hospital diagnoses we are certain that misclassification of disease status did not play a role in our findings.

Another area of concern in studies of passive smoking refers to the correct classification of study subjects with regard to exposure. In the present study, as in all others that have been published, the study subjects were classified based on the information on exposure obtained through interview. It is acknowledged that this approach is less than ideal. At the moment, however, it is the only feasible option. It has been suggested (as an alternative to interview) that laboratory measurements of cotinine in saliva or blood could be used to determine exposure. These would solve the problem only partially, because such techniques are unfit to measure exposure that has occured troughout a lifetime — a measurement that is necesary when studying

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a disease that probably occurs as a result of a prolonged exposure. Nevertheless, laboratory techniques can be used to validate and refine questionnaires that inquire about exposure.

The problem of recall posed by the use of questionnaires is magnified when the study subjects themselves are not available to provide the necesary information. In our study we had to resort to the use of surrogate respondents in 33.0 % of our interviews. In order to minimize problems arising from this approach we matched cases and controls on type of interview conducted, and obtained separate estimates of effect for self-respondents and surrogate respondents. The results, with only one exception (estimates of effect for number of years smoked by the spouse), did not differ on account of the individual who had provided the information. Similarly, Garfinkel (30) — who only used 12% of direct interviews — did not find significant differences among the different types of informers.

Environmental tobacco smoke has been for the past decades an ubiquituous pollutant to which everybody is believed to have been exposed in different degrees, whether knowingly or unknowingly. It has been suggested, therefore, that all studies on passive smoking suffer from misclassification of exposure since all claim to have identified individuals with zero exposure (that is, the individuals used as the non-exposed referent group). It is impossible to ascertain the degree to which such a problem may be present in our data, as it would be impossible to determine whether or not such a problem — if present — affected cases and controls equally. In the event of

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differential misclassification in our study, we would expect to find bias either away from or towards the null value. If, on the other hand, nondifferential misclassification affected our results, the bias could only be an attenuation of the estimates of effect. For such continuously measured variables as the ones assessed in this study, the magnitude of this bias would depend on the magnitude of the correlation between the true values for exposure and the values of exposure as measured.

We did not obtain information on certain variables known to affect exposure. Ventilation, size of room, proximity to the smoker and other conditions under which smoking takes place influence the actual dose received by the passive smoker. We acknowledge the difficulty in obtaining data in this regard, especially if information about a lifetime is been sought. We also beleived that asking for such extensive detail in a questionnaire might prevent our acquisition of more basic information, by distracting the interviewee from essentials. How these factors may have influenced our results can not finally be determined.

All our controls came from the files of the New York State Department of Motor Vehicles. We have data to support that they are comparable to the cases in the most relevent characteristics. There is, however, one potential source of problems. Whereas we are certain, by definition, that all controls were licensed drivers, we do not know the cases' status with regard to driving. If driving status is somehow related to the risk of lung cancer either directly or, much more likely, indirectly, our results might have been subject to bias.

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However, if any possible differences in driving status reflect only differences in socioeconomic status, our controlling in the analysis by INCOME should have taken care of the problem.

Of all the measures aimed to assess exposure to passive smoking, some measurement of the spouse smoking habits has been the most frequently used. This may account, at least partially, for the fact that this is also the measure most often reported to show a positive association with lung cancer risk. Among the different ways in which spouse smoking has been quantified, the number of cigarettes smoked per day appears most often in the literature. Number of packs a year smoked, total number of cigarettes smoked in a lifetime, number of years smoking, and number of cigarettes smoked at home have also been used as a proxy for exposure to passive smoking. In the present study we have chosen three different measurements of exposure: 1) number of cigarettes smoked a day by the spouse, 2) number of years the spouse smoked, and 3) total number of cigarettes smoked while married and living together. We beleive these three measurements comprise information on the two most important dimensions of exposure, intensity and duration. Additionaly they also provide results easily comparable to those in other studies.

Previous studies have shown that non-smoking women married to smokers of 20 or more cigarettes a day exhibit a risk of developing lung cancer that is approximately double the risk of those married to non-smokers (25,27,30). The estimates obtained in those studies have been reported to be significant, and when considered along with the

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estimates for other levels of exposure, have also been found to show a dose-response relationship, which further supports the case for a causal relationship. For a somewhat comparable level of exposure we were unable to detect any significant increase in lung cancer risk. Our point estimate of effect for those individuals married to smokers of 21-40 cigarettes/day was an odds ratio of 0.906 (95% CL: .609-1.35), when exposure was analyzed as a categorical variable. For higher levels of exposure we found risks above the null value, but again these findings were not statistically significant. The analysis of exposure data as a continuous variable was consistant with the above results; indeed the effect found for a differential of exposure of 20 cigarettes per day was barely above the null value (OR = 1.011), with confidence limits that include such a figure. Nor there was any evidence of a linear trend.

This report is not the only one that has been unable to confirm a statistically significant association between number of cigarettes smoked by the spouse and lung cancer risks. Akiba, et. al.(32) reported an odds ratio of 1.31 (90% CL: 0.48-3.47) for those exposed to spouse smoking of 20-40 cigarettes/day (reported as 140-279 cigarettes/week). For a similar level of exposure, Dalager et. al. (33) found an odds ratio of 1.5 (95% CL: 0.8-2.7). These latter estimates, although not significant, are within the range of the suspected magnitude of effect. A closer figure to our results, however, was reported by Garfinkel in his analysis of the American Cancer Society Study data (24). For exposure to spouse smoking of 20 or more cigarettes/day he found an odds ratio of 1.10. Similarly his results were not significant.

Our results regarding this variable cannot be accounted for by the inclusion of former smokers since any effect due to this circumstance would act in the opposite direction, that is, would inflate the risk attributable to exposure. Nor can it be explained by the use of surrogate interviews either, since no significant differences were found between the estimates for the latter and the estimates for self-respondents. The effect could not have been diluted by the inclusion of males, since they seem to show a similar response to that of women. Finally, unequal distribution in cases and controls regarding confounding variables cannot be responsible for the findings, as suggested by the minor change the estimates undergo when those variables are included in the analysis.

We did not find an effect dependant on the duration of exposure to passive smoking as measured by the number of years the spouse smoked while married and living together. Two other studies had evaluated the effect attributable to this measure of exposure. Dalager et. al. (33) reported non significant increases in risk due to spouse smoking of 1-20 years (OR = 1.73, 95% CL: .52-5.42), 21-30 years (OR = 1.78, 95% CL: .60-5.10), and >30 years (OR = 1.24, 95% CL: .42-3.53). These figures did not show evidence of a linear trend. Akiba, et. al. (32) reported odds ratios of 2.1 (90% CL: 1.0 - 4.3) for those married to smokers of 1-19 years, of 1.5 (90% CL: 0.8 - 2.7) for those exposed during 20-39 years, and an odds ratio of 1.3 (90% CL: 0.7 - 2.5) for those exposed to 40 or more years. These non significant effects did not show evidence of a linear trend. Garfinkel, et. al incorporated a different measure of duration of

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exposure. They estimated the effect associated with exposure due to husband's smoking in the last 5 and the last 25 years. These measures of exposure were analyzed for different age groups, histologic types, type of respondent, and socioeconomic status. Only one of 30 estimates obtained showed statistical significance (OR = 2.58 for members of the lower middle class exposed to spouse smoking in the last 5 years).

The evaluation of our third measurement of spouse smoking — total number of cigarettes smoked during married life — does not support an association with lung cancer risk. The estimate associated with a differential of exposure of 200,000 cigarettes was found to be 1.018 (95% CL: 0.877 - 1.18). Trichopoulous et. al. (27) used the same measurement to assess passive smoking. Their analysis, however, resulted in estimates that are relatively high (a three-fold increase in risk for exposure to 300,000 - 400,000 cigarettes), and which also show evidence of a linear trend. Their findings persisted after controlling for some important variables. In our study the inclusion of confounding variables did not produce any changes that would reverse our conclusion of a non significant association.

In the paragraphs above we have called attention to the fact that factors related to the design of the study, or to the presence of confounding variables, could not explain the differences between our results and those showing a positive association with spouse smoking. Other circumstances, however, may have affected our results. Some of these are presented as follows.

Critics of the first two epidemiologic studies on passive smoking raised the concern that the results carried out in two foreign countries (i.e. Japan and Greece) might not apply to the U.S. population. Exposure to spouse smoking, it was suggested, would not be as good a proxy measure for overall exposure to smoke in this country as it would be in those more traditional societies. In those societies spouse smoking — it is beleived — not only correlates well with overall exposure, but actually comprises a large proportion of it. A recent study in the U.S. suggests a different picture for this country. Friedman et. al. (92) have found that determining an individuals exposure on the basis of the spouse smoking habits may lead to gross errors. For instance, they reported that 47% of women and 39% of men married to smokers reported zero hours of exposure at home. Conversely, 40.5% of women and 49.2% of men married to non-smokers reported some exposure to the smoke of other persons. The degree in which a similar problem may apply to our data, or the way in which (if present) it may have affected our cases and controls differently, cannot be ascertained through the available information. Thus, such a possibility remains a potential source of error.

Different life conditions in the U.S. may also make the use of spouse smoking a bad proxy for exposure to passive smoking. For instance, the average Japanese home is much smaller than the American home. Two indicators of house size used by the United Nations illustrates this (93): 1) The average size, represented by the mean number of persons per household, is 3.2 in Japan, whereas in the U.S. is 2.7, and 2) the percentage of housing units with one room only is

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5% in Japan and 1.6% in this country. As mentioned in another section of this report, room size, together with a closely related variable — i.e. proximity to the smoker — greatly influence the exposure dose actually received by the passive smoker.

It might well be argued that, since some recent American studies have supported the findings of Hirayama and Thrichopoulous, objections such as those raised above have already been discounted. It should be emphasized, however, that only the study by Garfinkel et. al. has shown significant findings in the context of research without major methodological problems. An additional study (Pelayo Correa, et. al) presented questionable results, particularly due to the small number of subjects studied. Furthermore the most recent paper published in this country was unable to uncover any statistically significant association (Dalager, et. al.).

The effect due to spouse smoking in our study subjects may be so small as to be undetectable under the present conditions of study. Such effect, however, might well become detectable if exposure from different sources were to accumulate. The fact that we found an effect due to exposure in the household — which includes the spouse's smoking— strongly suggests this possibility. Sandler's findings further support it (37). He found an increase in risk with the increasing number of household members who smoked, including the spouse. Intuition, together with these results, would seem to suggest that the most appropiate way to evaluate the effect of passive smoking

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would be through the use of a cumulative index of exposure. Although in theory this is desirable, the exigencies of collecting the information may proscribe it. People's perception of the smoking that goes on around them may vary from one circumstance to another. Whereas people may be able to provide more or less detailed and accurate information on the smoking of the spouse or other members of the family, they might not be as precise when it comes to the smoking of others or to the smoking that ocurrs in public places. Combining such information in a single index could result in the mixing of "good" quality information with some "bad" quality information, thus diminishing the probabilities of finding good estimators of the effect.

Lastly, an explanation for our negative findings may be attributable to the fact that smoking by the spouse is an exposure that is introduced late in life and may not be prolonged enough to produce an effect in and of itself. Such exposure, however, could become important in the presence of a previous exposure history (i.e. parental smoking) or, as explained above, in conjunction with exposure from other sources.

We found an increase in risk for lung cancer for those exposed to the smoke of others at home. The odds ratio associated with 150 person/years of exposure was estimated to be 1.86 (95% CL: 1.22 - 2.83). Only a few previous studies have included a measurement of exposure at home as a risk factor to be evaluated. In such studies, however, the measurement of exposure has been rudimentary, usually

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expressed as a dicothomy (yes/no exposure). We believe our measurement to be more complete given that it comprises a proxy for the intensity of the exposure (number of smokers in the household), as well as for its duration (number of years of cohabitation with smokers). It can also be regarded as a comprehensive measure, since it includes all household members for the subjects' residence history (the latter expanding for the most part of their adult lives). The collection of such extensive information, however, was not without its problems, as evidenced by the ocurrence of some missing values. We have explained the ways in which we approached such problem (by imputation of missing values under two different assumptions) and feel confident that our results have not been substantially affected by it.

The following are the results from other studies assessing the role of exposure to passive smoking at home.

Garfinkel et. al (30) classified the exposure to smoke at home according to how recent was the exposure. For those exposed at home in the last five years (yes/no exposure) an odds ratio was found for lung cancer of 1.22 (95% CL: 0.92 - 1.62). An even lower estimate was reported for exposure in the last 25 years (OR = 1.15, 95% CL : 0.89-1.49). These results were not statistically significant, as shown by the confidence intervals. A more refined measurement of exposure at home was also assessed by Garfinkel, but it was limited to spouse smoking. A significant linear association was found for exposure to the spouse smoking at home (no association was found for the smoking that occurs outside the home). Sandler et. al. (37) reported an elevated risk for those exposed at home. The odds ratios associated

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with 1, 2, and 3 or more smoking household members were 1.5, 2.3 and 2.8, respectively. Even though only the last figure was in itself statistically significant, the three figures together follow a statistically significant linear trend. Kabat and Wynder (34) found no association between exposure at home (yes/no exposure) and risk for lung cancer. Their estimates, however, are based on a study that included only 25 lung cancer patients.

In addition to the overall effect due to household exposure found in our data, there is one other finding that deserves special consideration. The effect of passive smoking in the household was found to be significantly larger for epidermoid/small cell histologic type than for adenocarcinoma/other cells histologic type (unadjusted odds ratios of 2.83 and 1.42, respectively). Controlling for confounding variables resulted in estimates, that although not significant, were nonetheless consistent with the above findings (adjusted OR = 2.32, and 1.86, respectively). As explained in the paragraphs above, only a few studies have classified their cases in regard to histologic diagnosis, and even fewer have included a large enough number of cases of each histologic type as to be able to examine specific associations. The notion that passive smoking may be more strongly associated with epidermoid tumors, therefore, comes mainly from studies on the effects of direct smoking. Although some of these studies have determined that all histologic types are related to smoking (see Chapter 1: "Smoking and Histologic Type of Lung Cancer"), most of them seem to agree that the strongest relationship is observed for epidermoid and small cell tumors. The suggestion that

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such findings hold as well for passive smoking provides support to the hypothesis that environmental smoke acts in a similar way to mainstream smoke and that stresses that the only differences between the two types of exposures are quantitative. The one other study that found a statistically significant higher risk for epidermoid type was that of Garfinkel's et. al. (30). They reported an odds ratio of 5.0 (95% CL: 1.43 - 20.18) associated with the husband's smoking at home. Another study reported similar result, although non significant. Dalager et. al.(33) reported an adjusted odds ratio of 2.88 (95% CL: 0.91-9.10) for epidermoid/small cell carcinomas, and an odds ratio of 1.02 (95% CL: .33-3.16) for adenocarcinoma.

The importance of passive smoking in the household must be put into perspective with regard to the amount of exposure necessary to observe an effect of the magnitude described. We have presented the estimates of effects associated with an exposure of 150 person/years. This is equivalent to having lived over a period of 30 years with five smokers, or with approximately 4 smokers for 37 years. It should be emphasized that such level of exposure is rather high and may be uncommon in the general population. In our study group, for instance, only 7.5% of the cases and 4.3% of the controls attained that or higher levels of exposure. Indeed, lower levels of exposure are much more common. For example, 25% of the cases and 20.5% of the controls reported exposures between 50 and 75 person/years (equivalent to having lived 25 years with 2 or 3 smokers). Such levels of exposure, however, carry risks that are more modest (OR for 50 person/years = 1.23, for 75 person years = 1.36).

The exposure to passive smoking that occurs in the workplace has been thought to be extensive enough to deserve consideration as a potential risk factor for lung cancer. Laboratory data has shown that the urinary cotinine levels of non-smokers working where smokers are present are significantly higher than those of non-smokers working with non-smokers (56). The epidemiologic evidence has not been yet reported. Garfinkel found odds ratios of 0.88 (95% CL: 0.66-1.18) and 0.93 (95% CL: 0.73 - 1.18) for smoke exposure at work in the last 5 and 25 years, respectively (yes/no exposure classification). Kabat and Wynder found a barely statistically significant effect due to exposure at work (yes/no exposure) for males, but not for females. In their study 18 of 25 cases reported to have been exposed to cigarette smoke at work compared to 11 of 25 controls (OR = 3.27). In our study the risk associated with exposure in the workplace was statistically indistinguishable from the null value (OR = .9740, 95% CL: 0.974 - 1.014; for 150 person/years of exposure). We also found that exposure in the workplace may not be as extensive as beleived. Nearly a third of our cases and controls reported no exposure at all in the workplace, and almost 50% reported exposures of less than 25 person/years. This distribution results in a small number of highly exposed individuals in which the effect, although more likely to develop, would also be more difficult to detect. Finally, accumulation of exposure in the household and exposure in the workplace in a single measurement of exposure (both were measured in the same units) provided non significant results. We believed, as mentioned earlier in this chapter, that this is the result of combining two measurements with two different degrees of sensitivity. Whereas smoking by members

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of the family may be closely correlated with the dose received by the passive smoker, the correlation between co-workers' smoking and the dose received by the passive smoker may not be as close.

No other study before ours had included the assessment of exposure to passive smoking in social circumstances. We lack, therefore, any point of reference by which to compare our unexpected results. We found a decrease in risk for lung cancer with increased exposure to an index created to reflect social passive smoking (OR = 0.639, 95% CL: 0.520 - 0.785). Given all the following — 1) the previous reports that have shown an association between exposure to passive smoking and lung cancer, 2) our own results that support such relationship (at least for one of the exposure variables), 3) the studies that have established the association between active smoking and the disease, and 4) the laboratory data that has confirmed the carcinogenic properties of tobacco smoke — the possibility of a contradictory effect of passive smoking on lung cancer risks seems unfounded.

In searching for an explanation of this result, we must consider two possibilities: 1) that the association found reflects a true relationship, and 2) that the results are product of data artifacts. A third possibility, the role of chance, has largely been discounted through the application of tests for which the statistical significance has been set at 0.05 (i.e. results such as the ones observed may have occured as a consequence of chance only in 5 out of 100 "trials").

If we assume first that the relationship found between social exposure to passive smoking (as measured) and lung cancer is true, we well might wonder what could have caused lung cancer patients to have been exposed to less social passive smoking than were the "healthy" controls. Any response along those lines would be merely speculative; but the following is one that has occurred to us. Suppose that the cases have indeed developed the disease as a consequence of exposure to passive smoking. According to our results, the "causal" exposure would be the one derived from smoking in the household; that is, from the only exposure for which we found significant results. It could then be argued that the exposure which occurs in the home cannot be avoided (or cannot be easily avoided), whereas exposure in social circumstances is something over which the individual has a certain degree of control. If those who are to develop lung cancer develop early respiratory symptoms (as is suggested by the fact that lung cancer is often preceeded by a poor respiratory function [67]), they may choose to avoid exposure to smoke in social circumstances, but find it harder to do so at home. Thus, exposure in the household would continue to permit the disease-generation process to be completed, while at the same time exposure from other sources would be diminished. Similarly, it could be proposed that, in addition to passive smoking in the household, there is an as yet unidentified risk factor responsible for a considerable proportion of the cases. Increasing exposure to such a risk factor among the cases, however, would also have to be associated with a decreasing exposure to social passive smoking. In this way the reverse association observed between social passive smoking and lung cancer would be real, but by no means

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would be causal.

A second possibility we have considered is that our results regarding social exposure are artifactual. What is most likely responsible for this is the use of an artificial index of exposure not previously validated through proper methodologic studies. Some factors which may have affected the quality of the information collected through such mechanisms as follows. First of all, the period of time covered by the questionnaire items is very lengthy. Eliciting good information on day-to-day events in the past requires a considerable effort of recollection. Particularly for the first years of life, a considerable recollection of the parent's or the family's social life, which are the main vehicle of exposure to environmental smoke, is required.

Secondly, the information as it was collected did not make any attempt to measure intensity of exposure, nor did it establish the relative importance of exposure during one activity as opposed to another. There is a real question, for instance, if visiting friends or relatives who smoke conveys the same degree of exposure as would be incurred by going to bars and restaurants. Thus, exposure for all activities was weighted equally.

Thirdly, the specific social activities specified to the interviewee in order to elicit a response — that is, those representative activities known to be conducive to exposure — were very limited (see Appendix A, page 173). For many study subjects the

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exposure might originate from very different sorts of social circumstances than those explicitly questioned. The failure specifically to mention those activities may conceivably have produced some underreporting.

Fourth, the use of two different units of time to measure frequency of exposure may also have confused the respondents. The less frequent exposures had to be reported according to the number of times a month the exposure occured, whereas the most frequent exposures had to be reported on a per/week basis.

Finally comprehension of the information being requested may have been impaired by the complex nature of the questions. Each inquiry demanded responses which simultaneously synthetized information on three different aspects of exposure (type of social activity, age of exposure, and frequency of exposure). Such questions, placed almost at the end of a one hour interview, may have been answered without the concentration necessary to provide altogether adequate responses.

We have not mention in the above list the use of surrogate respondents as a possible source of data artifacts. The reason is that we do not have any evidence to support that the estimates obtained for self-respondents are any different from those of surrogate respondents (This is a situation that is also true for all of our exposure variables, with one exception: the number of years smoked by the spouse). But given the common concern on that matter, we felt that it should be made explicit.

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Imperfections of the data collection tools alone, however, may not be sufficient to explain our results. It is the way in which such imperfections affected the response of cases vis-a-vis the response of controls that may provide additional understanding. Again, we can only speculate on this matter. Our results suggest that the cases may have underreported their exposure to social passive smoking. Such a problem is often mentioned in relation to studies in which the suspected exposure is socially undesirable, as is the case with drug or alcohol use. In the present instance, however, there is no such stigmatization attached to exposure. It is, after all, the smoking of others, and not the patient's own risk factor that is being implicated. Nevertheless, patients for whatever reason may have felt the need to minimize their exposure to anything that potentially they might have been able to avoid. (Overreporting of exposure by controls may also, in theory, have produced the results observed. In practice, however, there is no compelling reason to beleive that controls would benefit from such behaviour. As a consequence we have discounted overreporting as a possibility).

Throughout this document we have presented a summary of the information currently available on the relationship between lung cancer and passive smoking. In the first part we have reviewed the major epidemiologic studies on the subject, as well as some relevant laboratory data. The major portion of this document, however, has been devoted to the description of the methodology and the results of this, largest epidemiologic study so far conducted to examine the

afore-mentioned association. Both the strengths and weaknesses of the study have been indicated; but when these are put into a balance, we beleive to have gathered one of the best data sets to judge the extense of the purported relationship.

We were unable to confirm an association with the most commonly used measure of exposure (spouse smoking), but we did find an effect due to exposure to passive smoking in the household. These results, although only in partial agreement with those of other studies, are consistent with the existence of a small to moderate effect of passive smoking on lung cancer risks. We did not find an effect due to exposure to passive smoking in the workplace. We found, however, a decreased risk in lung cancer with increasing exposure to passive smoking in social circumstances. Possible reasons for such findings have been discussed above.

Our findings suggest that the previous studies may have overestimated the effect attributable to passive smoking. Such a possibility has been proposed by those who contend that a typical exposure to passive smoking is only equivalent to smoking actively less than one cigarette per day (which in itself conveys risks that are lower than the two-fold increase proposed for passive smoking). Methodologic problems that may have led to such overestimation of the effect have been pointed out in Chapter 1, as well as in this chapter.

As is well known to epidemiologists, the results of one study — or even a few studies— are seldom sufficient to answer all questions

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regarding the relationship between a putative risk factor and a disease. We believe the present study has contributed to a better understanding of the lung cancer risk involved in the exposure to passive smoking. Nevertheless, we think we are still far from knowing all the details necessary to establish a final judgment. Future studies will be necessary to take that step.

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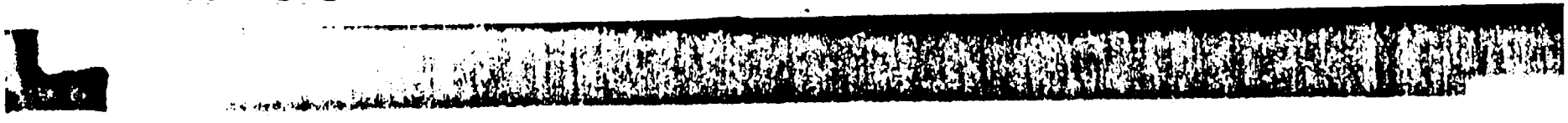

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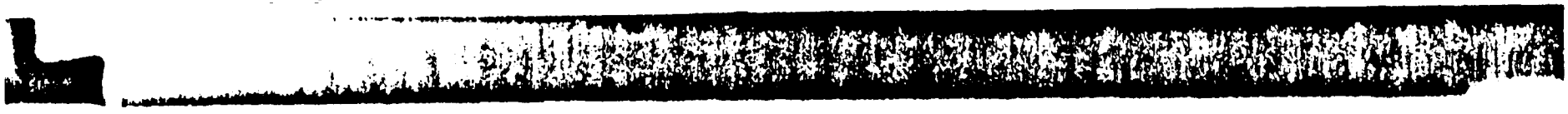

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Time Began /_/_/_/_/

Record # /1/ 1

(I) ID # /_/_/_/_/ 2 5

(C) Interviewer /_/_/ 6 7

(C) Date of Interview /_/_/_/_/_/_/ 8 13

(C) Length of Interview (minutes) /_/_/_/ 14 16

(b) Residence district /_/_/_/_/ 17 20

(D)(b) Sex /_/ 21
1. Male
2. Female

(C) Type of Interview /_/ 22
1. Individual
2. Surrogate: Spouse
3. Surrogate: child
4. Surrogate: sibling or parent
5. Surrogate: other

I'd like to begin by asking you a few general questions.

1. What is your date of birth? (D)(b) /_/_/_/_/_/_/ 23 30

2. In what country were you born? (RESIDENT CODES) (D) /_/_/ 29 30

_____

3. How many years of school have you completed? (CODE EXACT YEARS) (D) /_/_/ 31 32
12 - High School
16 - College Graduate
18 - Masters degree
20 - Doctorate

4. How tall are you? (CODE INCHES) /_/_/ 33 34
5' = 60"
6' = 72"

APPENDIX A

ITEMS IN THE QUESTIONNAIRE SELECTED FOR ANALYSIS

CODE:

(D) Sociodemographic variables

(b) Matching variables

(I) Outcome variables

(e) Exposure variables

(S) Confounding variables

(C) Quality control variables

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Record # /__/

ID # /__/__/__/__/

SMOKING HISTORY

FORMER SMOKERS ONLY (cases and controls) NON-SMOKERS SKIP TO PASSIVE SMOKING SECTION

Now I'd like to ask you a few questions about your smoking history.

21. How old were you when you first started smoking cigarettes on a regular basis, that is, at least one cigarette a day for at least a year? ⑥ /__/__/ 6

22. How old were you when you stopped smoking cigarettes on a regular basis? ⑥ /__/__/ 9

23. During those years did you ever stop smoking for more than one year? ⑥ /__/ 10

1. Yes --> A. During how many of those years were you not
2. No smoking? ⑥ /__/__/ 11 12

24. On an average, how many cigarettes per day did you usually smoke? ⑥ /__/__/ 13

(1 pack = 20 cigarettes)

25. Did you usually smoke filter, non-filter cigarettes, or both? ⑥ /__/ 15

1. Filter
2. Non-filter
3. Both

26. Did you inhale the smoke? ⑥ /__/ 16

1. Yes
2. No

ID # [ ][ ][ ][ ]

OCCUPATIONAL HISTORY

I'd like some information about each of the jobs or occupations you have had, including any jobs you may have held while in the armed services. You don't need to tell me about jobs that lasted less than a year or jobs you had while still in school. Let's start with the first one you had.

What was your job title?	What were your most important activities or duties	Name and location of employer	What did this business do?	What years did you work there?
	/__/__/__/ 70		/__/__/__/ 77 80	From /__/__/ to /__/__/ 89 91 92 93
	/__/__/__/ 96		/__/__/__/ 97 100	/__/__/ to /__/__/ 101 102 103
	/__/__/__/ 116		/__/__/__/ 117 119	/__/__/ to /__/__/ 121 122 123
	/__/__/__/ 136		/__/__/__/ 137 139	/__/__/ to /__/__/ 141 142 143
	/__/__/__/ 156		/__/__/__/ 157 159	/__/__/ to /__/__/ 161 162 163
	/__/__/__/ 176		/__/__/__/ 177 179	/__/__/ to /__/__/ 181 182 183
	/__/__/__/ 196		/__/__/__/ 197 199	/__/__/ to /__/__/ 201 202 203
	/__/__/__/ 216		/__/__/__/ 217 219	/__/__/ to /__/__/ 221 222 223
	/__/__/__/ 236		/__/__/__/ 237 239	/__/__/ to /__/__/ 241 242 243
	/__/__/__/ 256		/__/__/__/ 257 259	/__/__/ to /__/__/ 261 262 263
	/__/__/__/ 276		/__/__/__/ 277 279	/__/__/ to /__/__/ 281 282 283
	/__/__/__/ 296		/__/__/__/ 297 299	/__/__/ to /__/__/ 301 302 303

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IF YES: Did the building have a (1) basement or (2) crawlspace	Did any of these houses have a gas cooking range? (1) Yes (2) No	Were any of these houses heated by kerosene? (1) Yes (2) No	Were any of these houses heated with a coal or wood stove? (1) Yes (2) No	Did any of these houses have a kitchen fan that either blew cooking smoke or odors (1) outside or (2) inside?	Were any of these residences a mobile home or trailer (1) Yes (2) No
/_/ 15	/_/ 16 (S)	/_/ 17 (S)	/_/ 18 (S)	/_/ 19	/_/ 20
/_/ 30	/_/ 31 (S)	/_/ 32 (S)	/_/ 33 (S)	/_/ 34	/_/ 35
/_/ 45	/_/ 46 (S)	/_/ 47 (S)	/_/ 48 (S)	/_/ 49	/_/ 50
/_/ 60	/_/ 61 (S)	/_/ 62 (S)	/_/ 63 (S)	/_/ 64	/_/ 65
/_/ 75	/_/ 76 (S)	/_/ 77 (S)	/_/ 78 (S)	/_/ 79	/_/ 80
/_/ 90	/_/ 91 (S)	/_/ 92 (S)	/_/ 93 (S)	/_/ 94	/_/ 95
/_/ 105	/_/ 106 (S)	/_/ 107 (S)	/_/ 108 (S)	/_/ 109	/_/ 110
/_/ 120	/_/ 121 (S)	/_/ 122 (S)	/_/ 123 (S)	/_/ 124	/_/ 125
/_/ 135	/_/ 136 (S)	/_/ 137 (S)	/_/ 138 (S)	/_/ 139	/_/ 140
/_/ 150	/_/ 151 (S)	/_/ 152 (S)	/_/ 153 (S)	/_/ 154	/_/ 155
/_/ 165	/_/ 166 (S)	/_/ 167 (S)	/_/ 168 (S)	/_/ 169	/_/ 170
/_/ 180	/_/ 181 (S)	/_/ 182 (S)	/_/ 183 (S)	/_/ 184	/_/ 185

ID # [ ][ ][ ][ ]

PASSIVE SMOKING

27. Have you ever smoked any of the following?

	1. Yes 2. No	Age 1st Started	Current Smoker 1. Yes 2. No	Age Stopped	# Smoked per day	Inhale 1. Yes 2. No
(S) Cigars	17 /_/	18 /_/_/ 19	/_/ 20	21 /_/_/ 22	23 /_/_/ 24	/_/ 25
(S) Pipes	26 /_/	27 /_/_/ 28	/_/ 29	30 /_/_/ 31	32 /_/_/ 33	/_/ 34
(S) Marijuana	35 /_/	36 /_/_/ 37	/_/ 38	39 /_/_/ 40	41 /_/_/ 42	/_/ 43

28. Are you currently: (E) /_/ 44

(1) single (never married)
(2) married
(3) widowed
(4) divorced
(5) separated

(IF EVER MARRIED)

29. How many times have you been married? (E) /_/ 45

	1st	2nd	3rd	4th
30. How many years were you married and living together with your (1st, 2nd, 3rd, 4th) husband/wife? (E)	/_/_/ 46 47	/_/_/ 48 49	/_/_/ 50 51	/_/_/ 52 53
31. Did your (1st, 2nd, 3rd, 4th) husband/wife smoke during the time that you were married and living together? (E)	/_/ 54	/_/ 55	/_/ 56	/_/ 57
(1) YES --- A. How many cigarettes per day did he/she smoke? (E)	/_/_/ 58 59	/_/_/ 60 61	/_/_/ 62 63	/_/_/ 64 65
(2) NO B. How many years did he/she smoke when you were married and living together? (E)	/_/_/ 66 67	/_/_/ 68 69	/_/_/ 70 71	/_/_/ 72 73

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SOCIAL HISTORY

Now, I'm going to ask you about the amount of time you spent on some activities during certain periods of your life. I'd like you to answer using the responses on this card.

HAND CARD #1

ACTIVITIES	RESPONSES
1. Visiting in house of friends and relatives who smoked	0. Never
2. In bars or restaurants	1. 4 times a month
3. In any other activity that you recall being among people who smoked, such as bowling, playing bingo, in fraternal clubs and organizations, etc.	2. 1-3 times a month
	3. 1-3 times a week
	4. 4-7 times a week

Worksheet:

Fill Responses in the boxes, add, and note total.

Activities				Age		
1. ☐	2. ☐	3. ☐		1-10	ⓐ	186 /_/_/ 187
1. ☐	2. ☐	3. ☐		11-20	ⓐ	188 /_/_/ 189
1. ☐	2. ☐	3. ☐		21-30	ⓐ	190 /_/_/ 191
1. ☐	2. ☐	3. ☐		31-40	ⓐ	192 /_/_/ 193
1. ☐	2. ☐	3. ☐		41-50	ⓐ	194 /_/_/ 195
1. ☐	2. ☐	3. ☐		51-60	ⓐ	196 /_/_/ 197
1. ☐	2. ☐	3. ☐		61-70	ⓐ	198 /_/_/ 199
1. ☐	2. ☐	3. ☐		71-80	ⓐ	200 /_/_/ 201

ID # [ ][ ][ ] 1

32. Have you ever worked with dyes or pigments? /_/ 219

(1) YES (2) NO ③

33. Have you ever worked with substances which were very hot? /_/ 220

(1) YES (2) NO ③

34. Did any of the hobbies you have had ever involve any of the following?

(1) YES (2) NO

A. Woodworking ③ /_/ 221

B. Painting (house or furniture) /_/ 222

C. Glue /_/ 223

D. Garden Spray /_/ 224

35. Did any of the hobbies that you've had involve working with any toxic substances? ③ /_/ 225

(1) YES ---- Specify _____

(2) NO _____

_____

_____

- -

I have a few final questions.

36. What is your religious affiliation, if any? ⑧ /_/ 226

(1) Catholic
(2) Protestant
(3) Jewish
(4) Other _____
(5) None

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ID # ☐☐☐☐

HOME CARD #2

37. Which of these categories best describes your total household income last year before taxes? (E) /_/_/ 227 228

01-A	Under $4,000	06-F	16,000 - 18,999
02-B	4,000 - 6,999	07-G	19,000 - 21,999
03-C	7,000 - 9,999	08-H	22,000 - 24,999
04-D	10,000 - 12,999	09-I	25,000 - 29,999
05-E	13,000 - 15,999	10-J	Over $30,000

WOMEN ONLY

38. Did you ever take oral contraceptives? /_/ 229

(1) Yes ——— A. How many years did you take them? 230 /_/_/ 231
(2) No

RACE OBSERVATION: Ethnic Category (E) /_/ 232

(1) White
(2) Black
(3) Oriental
(4) Other
(9) Unknown

Is there anything else about your background or past history that you think is important to this study, even if I didn't specifically ask about it?

_____

_____

_____

_____

Time ended /_/_/_/_/

ID # ☐☐☐☐

CHEMICAL EXPOSURES

Now, I'd like to ask you about substances you may have been exposed to. I'm going to read you a list of materials, many of which may sound unfamiliar to you. But if you have had a job, military duty or hobby that involved any of these substances, you will probably recognize the name when I read it. Have you ever been exposed to:

(1) YES (2) NO IF YES: PLEASE EXPLAIN

A.	Asbestos	(S)	/_/ 202
B.	Asphalt	(S)	/_/ 203
C.	Arsenic	(S)	/_/ 204
D.	Beryllium	(S)	/_/ 205
E.	Chromium or Chromates	(S)	/_/ 206
F.	Formaldehyde	(S)	/_/ 207
G.	Chloromethyl ether	(S)	/_/ 208
H.	Soy dust	(S)	/_/ 209
I.	Herbicides (such as Agent Orange)	(S)	/_/ 210
J.	Nickel	(S)	/_/ 211
K.	Mustard gas	(S)	/_/ 212
L.	Plastics	(S)	/_/ 213
M.	Polyvinyl chloride	(S)	/_/ 214
N.	Any type of radiation	(S)	/_/ 215
O.	Uranium	(S)	/_/ 216
P.	Sand	(S)	/_/ 217
Q.	Sprays for orchards or vineyards which contain arsenic	(S)	/_/ 218

Source: https://www.industrydocuments.ucsf.edu/docs/flyx0000

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